FDA Executive Summary

Prepared for the
October 26, 2011 meeting of the
Circulatory System Devices Panel

P100046
AtriCure Synergy Ablation System
AtriCure, Inc.

Introduction

This is the FDA Executive Summary for the AtriCure Synergy Ablation System. This device is a surgical ablation device intended to treat atrial fibrillation in patients undergoing concomitant open heart surgery. A clinical trial to study the device was approved by the agency on June 8, 2007 under IDE G070080. AtriCure, Inc. (the Sponsor) has most recently submitted a Pre-Market Approval (PMA) application for marketing approval of the device (P100046). This submission has been reviewed by the Division of Cardiovascular Devices (DCD) within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This memorandum will summarize FDA's review of the PMA up to this point, highlighting the particular areas for which we are seeking your expertise and input. These topics will include the proposed indications for use and the results of the clinical study conducted by the Sponsor.

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1 PROPOSED INDICATIONS FOR USE

The AtriCure Synergy Ablation System is intended to ablate cardiac tissue for the treatment of persistent or longstanding persistent atrial fibrillation in patients who are undergoing open concomitant coronary artery bypass grafting and/or valve replacement or repair.

Note that this device is commercially available and has been cleared through the 510(k) process for the "ablation of cardiac tissue." The purpose of this PMA is to request approval for a specific claim of treatment of atrial fibrillation (AF).

2 DEVICE DESCRIPTION

The AtriCure Synergy Ablation System is used during cardiac surgery to create lesions in the myocardium in a specific pattern, to direct cardiac electrical propagation such that re-entry cannot occur and fibrillation cannot be established. Lesions are created through radiofrequency (RF) ablation, whereby application of electric current in the RF range results in local tissue heating around the electrode and subsequent tissue death due to protein coagulation. Lesions formed with RF ablation block the conduction of cardiac electrical activity. To treat atrial fibrillation (AF), specific lesions are placed in the right and left atria according to a pattern called the "Maze IV" (see Section 6.9, Figure 4 and Figure 5).

The AtriCure Synergy Ablation System consists of the following components:

- Ablation and Sensing Unit (ASU) – generates RF energy and senses tissue impedance, controlling the ablation cycle.
- Isolator Switch Matrix (ASB) – allows the user to connect multiple AtriCure handpieces to the ASU.
- AtriCure Synergy Ablation Clamps (models OLL2, OSL2) – clamp atrial tissue between their jaws in order to apply RF energy

The AtriCure Synergy Ablation Clamps are connected through an integral cable to the ASU. The ASU and ASB are connected via a short cable and these units provide and direct RF energy to the Clamps. For details of the operation of the system components, please see the Sponsor's executive summary. The system components are depicted in Figures 1 through 3.

Figure 1. Synergy Ablation Clamp

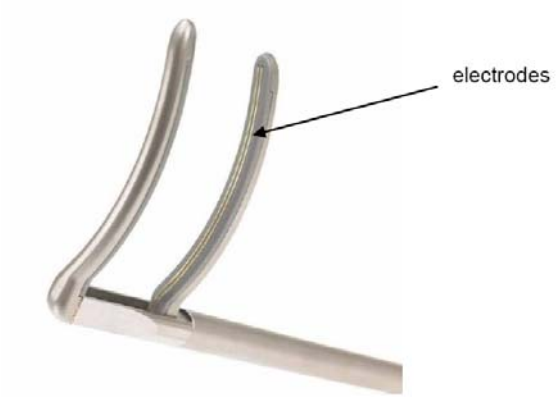

Figure 2. Synergy Ablation Clamp End Effector.

Figure 3. ASU and ASB

3 REGULATORY HISTORY

The AtriCure Synergy Ablation System was cleared under premarket notification (510(k)) K063630 on January 26, 2007 for the following indication: *The AtriCure Ablation System is intended to ablate soft tissues during general surgery using radiofrequency energy.* Subsequently, the Sponsor submitted a 510(k) (K101174) to expand the indication for the system to be: *The AtriCure Bipolar System including Synergy Dual Electrode Clamps is intended for the ablation of cardiac tissue during surgery.* This 510(k) was cleared on November 12, 2010. Although the trade names of the system differ between the submissions, the system under review in this PMA is identical to the devices currently marketed under K063630 and K101174. The purpose of this PMA is to expand the

indications for use to include the specific claim of treatment of persistent or longstanding persistent AF in the concomitant surgery setting.

The Sponsor submitted its first original IDE (G020237) for an expanded label claim to include treatment of "continuous" AF on September 16, 2002. This study, the RESTORE trial, was fully approved on December 19, 2003 for 15 centers and 226 subjects. The RESTORE trial, which used an ablation system similar to the AtriCure Synergy Ablation System, encountered significant enrollment difficulties and suspended enrollment after three years with a total of 39 treated and 5 matched concurrent control subjects. The study design for RESTORE is discussed in more detail below.

Due to the low enrollment in the RESTORE trial, the Sponsor submitted a new IDE (G070080) in May 2007. The "ABLATE" trial was granted full approval on September 6, 2007. The ABLATE study is described below and was designed to facilitate collection of data to support the safety and effectiveness of the AtriCure Synergy Ablation System in the treatment of permanent[*] AF at a time when obtaining such data was particularly challenging due to the extensive off-label use of the device for the treatment of AF. The first patient was enrolled on February 8, 2008.

The Sponsor conducted the pre-specified interim analysis for the ABLATE study when 55 patients had been enrolled and followed for 30 days and 29 patients had been followed for 6 months. The interim analysis found that that the predictive probability for trial success was 98.8%, which was greater than the pre-specified threshold rate of 90% for a test at 55 subjects. Given these results, the criteria for stopping enrollment in the study had been met and no further subjects were enrolled.

The Sponsor and FDA met on October 14, 2009 to discuss PMA filing. At this and subsequent meetings, FDA indicated that the ABLATE dataset is small and that additional data sources would be helpful to support their PMA application. The Sponsor proposed (1) to obtain longer term data for their RESTORE and ABLATE subjects, (2) to obtain safety and effectiveness data from additional subjects in a secondary registry (ABALTE AF), and (3) to present data on the use of their device from two institutional databases (Washington University and Baylor-Plano). After some negotiation, FDA agreed to these proposals.

The Sponsor submitted its PMA P100046 to FDA on December 24, 2010. A major deficiency letter was sent to the Sponsor on March 24, 2011. The Sponsor submitted its response, the subject of this current review, on June 9, 2011 in Amendment 002. No additional official submissions have been made after that, although interactive review is ongoing.

[*] Permanent AF as defined in the 2006 AHA/ACC/ECAS Practice Guidelines (Fuster et al., 2006, Circulation, 114, e257-e354.).

FDA Commentary: Over the last ten years enrollment in surgical AF ablation studies has been challenging. Initially, FDA advocated study designs where subjects indicated for cardiac surgery would be randomized to receive either optimum medical therapy or ablation to treat their AF. However, there seemed to be a lack of equipoise on the part of study subjects and investigators such that neither was willing to participate in a study where a subject scheduled for cardiac surgery might not receive ablative treatment. AtriCure also attempted to conduct a study (RESTORE) where matched control subjects in normal sinus rhythm would be enrolled concurrently with the subjects treated with the investigational device. It became evident after concerted efforts to enroll subjects in these studies, that it would not be feasible to execute either study design. Consequently, FDA worked with AtriCure to develop a non-randomized study with endpoints based on performance goals - the ABLATE study.

4 PRE-CLINICAL AND ANIMAL STUDIES

The Sponsor has conducted *in-vitro* bench and animal studies of the AtriCure Synergy Ablation System. FDA reviewed extensive pre-clinical testing including:

- Biocompatibility testing
- Electrical, mechanical, and environmental *in-vitro* bench testing
- Sterilization testing
- Packaging and Shelf-life testing
- Animal testing

Please see the Sponsor's executive summary for a list and description of the tests conducted.

FDA Commentary: FDA has no remaining concerns with regard to pre-clinical testing of the device.

5 PRIOR CLINICAL EXPERIENCE

As indicated above the AtriCure Synergy Ablation System was cleared for US marketing in January 2007. The AtriCure Synergy Ablation System first received the CE Mark in March 2007 for ablation of soft tissue, with CE Mark approval updated for the treatment of cardiac arrhythmias including atrial fibrillation in February 2008. The AtriCure Synergy Ablation System is approved for commercial distribution in the United States, European Union, Canada, Japan, Lebanon, Colombia, Panama, Ecuador, Peru, China, Hong Kong, Argentina, Chile, Brazil, Thailand, Australia, Mexico, Turkey, Georgia, Azerbaijan, Russia, Norway, Taiwan, Costa Rica, Korea, Lithuania, Vietnam, and Malaysia.

Although not approved in the US for treatment of atrial fibrillation, its widespread use for that purpose is evident in the literature. The first literature report appeared in 2002,[*] in which 120 patients underwent ablation with a predecessor of the AtriCure Synergy Ablation System device during mitral valve surgery.[†] Since that time, most published papers on the AtriCure ablation systems have focused on patients undergoing concomitant surgery, with a few reports of patients undergoing treatment for lone (isolated) AF, either through the open chest or minimally invasive, closed-chest approaches.

The patient populations in these published reports are quite heterogeneous, with 25-50% having paroxysmal AF, 25-33% persistent AF, and 33-67% permanent AF (see Table 1). Furthermore, success rates at achieving freedom from AF vary widely, anywhere from 58% to 91%, and with different definitions of "freedom". Effectiveness is also reported over widely variable periods of follow-up (3 months to 1 year) and with many different methods of rhythm determination (ECG, Holter monitor, pacemaker interrogation, and loop recorders).[‡]

Reference	Concomitant Procedure(s)	Subjects	Paroxysmal AF	Persistent AF	Permanent AF	Freedom from AF @ Follow-up Time
Akpinar 2006	CABG	33	36%		64%	Permanent: 58.1% @ 6 mos
Beyer 2009	Lone MIS	100	39%	29%	32%	Persistent & permanent: 96% & 71% @ 13.6 mos
Doty 2007	CABG, MVR, AVR, tricuspid	65	32%		68%	All: 79.6% @ 6 mos
Edgerton 2006	Lone MIS	47	74%		26%	Permanent: 71.4% @ 6 mos
Edgerton 2010	Lone MIS	52	100%			Paroxysmal: 86.3% @ 6 mos
Gillinov 2004	MVR	108	25%	26%	49%	All: 85% @ 3 mos
Melby 2006	Lone 32%, Concomitant 68%	100	59%	7%	34%	All: 91% @ 12 mos
Mokadam 2004	57% Lone, 43% Concomitant	30	63%	37%		All: 96% @ 12 mos
Sternik 2010	MVR	192	15%	39%	46%	All: 86% @ 6 mos
Sternik 2006	Lone	60		54%	46%	All: 80% @ unknown time
Suwalski	Lone	6	100%			3 pts: 100% @ 3

[*] Gillinov and McCarthy, 2002, Ann Thorac Surg, 74, 2165-8 discussion 2168

[‡] Gillinov and McCarthy, 2002, Ann Thorac Surg, 74, 2165-8 discussion 2168; Gillinov et al., 2004, Heart Surg Forum, 7, E147-52; Melby et al., 2006, J Cardiovasc Surg (Torino), 47, 705-10; Melby et al., 2006, Ann Surg, 244, 583-92; Srivastava et al., 2008, Heart Lung Circ, 17, 232-40; Weimar et al., 2011, J Interv Card Electrophysiol, 31, 47-54; Ip et al., 2011, J Interv Card Electrophysiol

Reference	Concomitant Procedure(s)	Subjects	Paroxysmal AF	Persistent AF	Permanent AF	Freedom from AF @ Follow-up Time
2007						mos
Weimar 2011	Lone	100	31%	6%	63%	All: 93% @ 6 mos

"MIS" = Minimally invasive surgical technique
"Lone" = Treatment only for atrial fibrillation; no concomitant procedure
"Concomitant" = any or all of CABG, MVR, AVR, tricuspid

Table 1. Published Reports of Surgical Ablation Studies

Therefore, despite the pervasive use of the AtriCure ablation systems, the literature does not provide an unambiguous assessment of safety and effectiveness of the device for the purposes of supporting the Sponsor's proposed marketing application.

FDA Commentary: Despite widespread use for the specific purpose of treating AF, published literature reports are limited by their heterogeneity and lack of standardized follow-up and reporting.

6 IDE CLINICAL STUDY

The ABLATE trial ("AtriCure Synergy Bipolar RF Energy Lesions for Permanent Atrial Fibrillation Treatment during Concomitant, On-Pump, Endo/Epicardial Cardiac Surgery") was designed to evaluate the safety and effectiveness of the AtriCure Synergy Ablation System in the treatment of permanent AF in the setting of certain concomitant open-heart surgeries, such as coronary artery bypass grafting and/or valve repair or replacement. This pivotal study was a single arm, multi-center, prospective, non-randomized clinical trial based on a Bayesian adaptive design. As noted above, FDA found the single-arm study design to be acceptable due to the Sponsor's difficulty in enrolling control (i.e. not-ablated) patients in the RESTORE trial, a previous IDE study designed to show safety and effectiveness of an earlier version of the AtriCure Bipolar System.

The Sponsor proposed performance goal endpoints based on historical data reported in the clinical literature and its own RESTORE trial. These performance goals are discussed below. The primary effectiveness endpoint for the ABLATE study is the rate of patients who are free of atrial fibrillation and not taking anti-arrhythmic drugs (AADs) 6 months after the procedure. The primary safety endpoint is the rate of 30-day/in-hospital death, stroke, myocardial infarction (MI), transient ischemic attack (TIA), or bleed (a composite endpoint). Additional details on these endpoints are presented below.

Enrollment was targeted to be between 50 and 100 subjects at 20 sites. The study utilized a Bayesian adaptive approach to sample size determination that included an interim analysis of the primary safety and effectiveness endpoint data in order to determine the point of enrollment cessation.

6.1 Statistical Aspects of the Study Design

Statistical evaluation of primary outcomes was performed using Bayesian methodology for all analyses (interim, for sample size determination, and final). These are described briefly below.

6.1.1 Primary Safety Analysis

The primary safety endpoint was the rate of MAEs (death, stroke, MI, TIA or bleed) occurring within the initial 30 days post procedure or discharge (whichever is later). The statistical hypothesis for safety is

$$q_T < 0.1895,$$

where the treatment adverse event rate is labeled q_T. The primary safety endpoint would be considered met if the posterior probability that q_T is less than 0.1895 exceeds 0.95, i.e.

$$\Pr(q_T < 0.1895 \mid \text{Trial Results}) \geq 0.95.$$

The value 0.95 is chosen to achieve 0.05 overall type I error rate for safety. The prior distribution for the primary safety endpoint is Beta (1,1). The choice for the performance goal 0.1895 is discussed below in Section 6.4.

6.1.2 Primary Effectiveness Analysis

The primary effectiveness endpoint is the rate of subjects that achieved successful obliteration of atrial fibrillation while off of any antiarrhythmic medication (Class I or III) evaluated at six months post procedure. The statistical hypothesis is

$$p_T \geq 0.60,$$

where p_T is the probability of being a success for effectiveness. The primary effectiveness endpoint would be considered met if the posterior probability that p_T is greater than 0.60 exceeds 0.975, i.e.,

$$\Pr(p_T > 0.60 \mid \text{Trial Results}) \geq 0.975.$$

A uniform prior distribution is assigned for the unknown probability of success, p_T~ Beta(1,1). The value 0.975 is chosen to achieve 0.025 overall type I error rate for effectiveness. The choice for the performance goal 0.60 is discussed below in Section 6.6.

6.1.3 Interim Monitoring and Adaptive Design

The Sponsor used a Bayesian adaptive approach to sample size selection. The minimum total sample size was 50 patients and the maximum was 100.

The first interim look was to be made when 50 patients had been enrolled in the study and 20 patients had reached their 6-month endpoint, whichever occurred later. This was to be repeated after every five patients were enrolled until the threshold for enrollment cessation was achieved, for a maximum of 10 interim analyses.

At each interim analysis the Sponsor was to calculate the predictive probability of meeting the primary safety and the primary effectiveness endpoint at the end of the trial. The predictive probability of meeting the effectiveness endpoint and the safety endpoint is calculated two ways: first assuming accrual stops and all currently enrolled patients are followed to six months, second assuming enrollment continues to the maximum sample size, 100 patients, and all are followed to six months. Because the final outcomes of some enrolled subjects were not yet known at the time of the interim look, they were predicted, using information from the subjects with known outcomes, in combination with a beta-binomial distribution for modeling the transition from either baseline or 3-month outcomes to the 6-month outcomes. The predictive probability was used to decide whether (1) to stop accruing patients, wait 6- months, and then do the final analysis, (2) to stop the trial for futility, or (3) to continue enrolling subjects into the trial. The predictive probability thresholds for stopping enrollment began at 90%, and then decreased gradually to 80% as the maximum sample size was reached. The futility thresholds began at 5% and increased to 10%.

Note that predictive probability is only used to decide whether to stop enrollment or stop for futility. It is not used for making a decision about the final analysis. The final analysis will use 6-month data from all enrolled patients, with no predicted patients.

6.1.3.1 Control of Type I Error Rate

The type I error rate may be inflated in a statistical design that incorporates interim monitoring. For the ABLATE study, the Sponsor calculated the type I error rate jointly for the primary safety endpoint and the primary effectiveness endpoint. However, FDA currently believes that the type I error rate should be controlled independently at a desired level for the primary safety endpoint (5% for this study) and for the effectiveness endpoint (2.5% for this study). Therefore FDA conducted its own simulations to calculate the type I error rate for each primary endpoint (safety and effectiveness) independent of the other primary endpoint. The results showed that the type I error rate for the primary safety endpoint was controlled at 5%. However, the type I error for the primary effectiveness endpoint was inflated from 2.5% to 3.5%. Given the current design scheme, if the type I error rate for the primary effectiveness endpoint was controlled at 2.5%, the corresponding posterior probability criterion for the primary effectiveness endpoint at the final analysis would be 0.977, instead of 0.975 as specified in the protocol.

FDA Commentary: Although FDA currently believes that the type I error rate should be controlled independently for the primary safety and effectiveness endpoints, FDA notes that the study conclusions and analyses presented herein are not affected by the inflation of the type I error observed for the primary effectiveness endpoint when calculated in this manner.

Please refer to the Sponsor's executive summary and supporting appendices for full details on calculation of predictive probability and other aspects of the statistical design of the ABLATE study.

6.2 Key Inclusion/Exclusion Criteria for Primary Study Population

The inclusion and exclusion criteria for the ABLATE study are summarized in the Sponsor's executive summary. Key inclusion criteria include history of permanent AF according to the 2006 ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation[*] and need for elective cardiac surgical procedures performed on cardiopulmonary bypass including mitral valve repair/replacement, aortic valve repair/replacement, tricuspid valve repair/replacement, and coronary artery bypass grafting. Notable exclusion criteria were any previous cardiac ablation (including catheter ablation), left atrial diameter greater than or equal to 8 cm, and/or the use of inotropes or an intra-aortic balloon pump prior to surgery.

6.3 Analysis Populations

As background for discussion purposes, it is helpful to present the definitions for AF classification according to the 2006 ACC/AHA/ESC Guidelines and 2007 HRS/EHRA/ECAS Expert Consensus Statement[†]. These are presented in the table below. The Sponsor used definitions in the 2006 ACC/AHA/ESC Guidelines in designing and executing the ABLATE study; however, since ABLATE began, these definitions were refined in the 2007 HRS Statement.

AF Classification	2006 ACC/AHA/ESC Guidelines	2007 HRS Statement
Paroxysmal	AF is self-terminating within 7 days of recognized onset	Recurrent AF (>2 episodes) that terminates spontaneously within 7 days
Persistent	AF is not self-terminating within 7 days, or is terminated electrically or pharmacologically	AF which is sustained beyond 7 days, or lasting less than 7 days but necessitating pharmacologic or

[*] Fuster et al., 2006, Circulation, 114, e257-e354.
[†] Caulkins et al., 2007 Europace, 9, 335-379.

AF Classification	2006 ACC/AHA/ESC Guidelines	2007 HRS Statement
		electrical cardioversion
Longstanding Persistent		Continuous AF of greater than one-year duration
Permanent	AF in which cardioversion (electrical and/or pharmacologic) has failed or has not been attempted	Patients where a decision has been made not to pursue restoration of sinus rhythm by any means

Table 2. AF Classification per 2006 ACC/AHA/ESC Practice Guidelines and 2007 HRS Statement

ABLATE was originally designed to assess the safety and effectiveness of the AtriCure Synergy Ablation System in the treatment of subjects with permanent AF as defined by the 2006 ACC/AHA/ESC Guidelines. The term "permanent" was essentially abandoned in 2007 with the publication of newer guidelines from the Heart Rhythm Society. FDA has generally interpreted "permanent" AF to indicate continuous atrial fibrillation of long-standing duration. In the initial round of review of this PMA, it became apparent that the population studied did not align with the population expected by FDA for this study of "permanent" AF.

FDA Commentary: ABLATE was originally designed to assess the safety and effectiveness of the AtriCure Synergy Bipolar Ablation System in the treatment of subjects with *permanent* AF as defined in 2006, a term which was essentially abandoned in 2007. FDA notes the following:

1. FDA now typically associates the previous "permanent" designation with the contemporary AF classification "longstanding persistent."
2. In their original submission, the Sponsor argued that patients with a long history of AF and associated comorbidities (*e.g.*, enlarged left atria) could be considered "permanent", even if the AF were self-terminating, paroxysmal AF. FDA does not agree with this argument and believes that "permanent" (per 2006 Guidelines) implies continuous, non-self-terminating AF of duration at least one year, or that has failed cardioversion.

This change in terminology resulted in some confusion at the time the PMA was submitted, and after several discussions between the Sponsor and FDA it was decided that a re-focusing of the target population was required. The Sponsor sought an indication to treat patients with "continuous" forms of AF and not "intermittent", or "paroxysmal". Therefore, as part of the application review process, the Sponsor contracted with two physicians expert in the field of AF to review the supporting documentation for each of the subjects enrolled in ABLATE as well as the other data sources. They re-categorized each subject as having either "paroxysmal", "persistent",

or “long-standing persistent” AF according to 2007 HRS Statement. Based on this review, four subjects were re-classified as “paroxysmal.” The Sponsor has proposed an indication that includes both persistent and long-standing persistent AF, and proposes to exclude patients with paroxysmal AF from the labeling to support this indication.

In this executive summary, results from two populations are presented: (1) the Treated population, which includes all enrolled patients treated with the device, including those patients re-classified as having paroxysmal AF, and (2) the Non-Paroxysmal AF population, which includes only those patients classified as having persistent or longstanding persistent AF.

FDA Commentary: Historically, FDA has required separate studies for indications of paroxysmal AF, persistent AF and longstanding persistent AF. The studies recommended for the different types of AF differ with regard to the extent of monitoring of AF status and to the duration of follow up. For example, a study that enrolls subjects with long-standing persistent AF may require a shorter overall study duration and less frequent, possibly less rigorous (e.g. ECG instead of Holter) monitoring than a study for persistent AF or paroxysmal AF. Thus, at the time that the IDE for this study was submitted to the Agency, FDA would have expected the Sponsor to conduct separate studies for persistent AF and “permanent” (2006 definition)/long-standing persistent AF studies.

The Sponsor contends that from a mechanistic and treatment perspective, it is reasonable to combine persistent and longstanding persistent AF into a single category, separate from paroxysmal AF. FDA has no strong objection to this perspective. FDA also believes that the rigor of monitoring of AF status and duration of follow-up for the ABLATE study patients are acceptable for both persistent and long-standing persistent forms of AF. FDA is interested in panel input on the appropriateness of combining these two groups and excluding the category of paroxysmal AF.

6.4 Primary Safety Endpoint

The primary safety endpoint was the rate of Major Adverse Events (MAEs) occurring within the initial 30 days post procedure or discharge (whichever is later). The MAEs consist of: death, excessive bleeding (defined as > 2 units of RBCs with reoperation), stroke, transient ischemic attack (TIA) or myocardial infarction (MI). The Sponsor derived a historical safety rate of 13.95% from the reported experience with the “cut and sew” Cox Maze III procedure. A performance goal of 18.95% was used for hypothesis testing. The primary safety endpoint would be considered met if the Bayesian posterior probability that the rate of MAE is less than 18.95% exceeded 0.95.

FDA Commentary: In a study of concomitant surgery, the morbidity of the open heart procedure very likely overwhelms the morbidity inflicted by the device. This is distinct

from a study of lone ablation, and is important in evaluating the risk/benefit profile of the device.

6.5 Secondary Safety Endpoints

There were two secondary safety endpoints. These were not tested for statistical significance, and were reported only in descriptive form. They were:

- Composite 6-month major adverse event rate; and
- Overall 6-month adverse event rate.

6.6 Primary Effectiveness Endpoint

The primary effectiveness endpoint was defined as the rate of subjects that are free of AF while off of any antiarrhythmic medication (Class I or III) evaluated at six months post procedure via 24-hour Holter monitor assessment (or permanent pacemaker interrogation in the case of those subjects that have a pacemaker implanted). The Sponsor identified a reference rate of 70% based on surgical ablation procedures performed using RF ablation technology in the setting of concomitant surgery as found in historical literature, as well as its own RESTORE IDE study. A performance goal of 60% was used for hypothesis testing. The primary effectiveness endpoint would be considered met if the Bayesian posterior probability that the six-month success rate is greater than 60% exceeds 0.975.

Freedom from AF was defined as episodes < 5 minutes duration and no more than 1 hour total AF duration in 24 hours.

FDA Commentary: As the definition of freedom from AF has changed with the adoption of the 2007 HRS Statement, the Sponsor was asked to provide post hoc analyses defining "freedom of AF" as freedom from episodes of AF, atrial tachycardia, and atrial flutter greater than 30 seconds.

6.7 Secondary Effectiveness Endpoints

There were three secondary effectiveness endpoints. These were not tested for statistical significance but rather reported only in descriptive form. They were:

- The proportion of subjects free of AF *independent* of the need for anti-arrhythmic drugs as determined by 24-hour Holter recording at 6-months;
- Effectiveness of pulmonary vein isolation as determined by intraoperative pacing; and
- Overall AF burden (% of 24 hours) measured by 24-hour Holter monitor at 6-months

6.8 Additional Supportive Analyses

In addition to the pre-specified primary and secondary endpoints, the Sponsor conducted the following additional analyses to support the primary analyses

- Rate of pacemaker implantation (pre-specified in the protocol),
- The proportion of patients in the treatment group who are free of AF and off Class I and III antiarrhythmic drugs as assessed by a 48-hour Holter recording performed at a minimum of 12 months post procedure,
- The proportion of patients in the treatment group who are free of AF independent of the need for anti-arrhythmic drugs (Class I and Class III) as assessed by a 48-hour Holter recording performed at a minimum of 12 months post procedure, and
- Overall AF burden in the treatment group measured on a 48-hour Holter recording at 12 months or after.

FDA Commentary: Data regarding AF status at 12 months or greater was requested by FDA to align with current follow-up recommendations to determine freedom from AF, as set forth in the 2007 HRS Statement. Collection of this data was not part of the original protocol and was added in 2010 after enrollment in the study had been stopped to more rigorously assess the durability of treatment as added support of the data for this PMA. FDA believes that collection of data at 12 months in addition to 6 months helps to support inclusion of patients with persistent AF in the indicated population.

6.9 Study Procedures

The following presents a brief overview of the key study procedures. Although the specific order and details of the procedures will depend on the concomitant surgery being performed, the following description outlines an example of the procedural flow. Please see the Sponsor's executive summary for additional details.

The operating surgeon identified potential subjects, usually after consultation for a cardiac surgical procedure. Subjects were then screened according to the inclusion and exclusion criteria. Pre-treatment demographic data were gathered.

At the time of treatment, investigators were required to perform the Maze IV procedure[*] using the investigational system. Briefly, the chest was opened, the patient was placed on cardiopulmonary bypass, and the heart arrested. First the left atrial Maze IV epicardial lesions were created. These included both right and left pulmonary vein

[*] Damiano et al., 2011, J Thorac Cardiovasc Surg, 141, 113-21; Shen et al., 2009, Innovations (Phila), 4, 248-255; Weimar et al., 2011, J Interv Card Electrophysiol, 31, 47-54

isolation as well as a series of ablation lines along the roof and floor of the posterior left atrial wall to create a complete "box" (see Figure 4). Additional endocardial lesions were performed from the box onto the posterior mitral valve annulus. On the right side of the atrium (Figure 5), lesions were performed epicardially along the right anterior free wall to the atrial appendage, as well as endocardially from the appendage to the tricuspid annulus, and from the superior vena cava (SVC) to the inferior vena cava (IVC). Confirmation of exit block was then performed to assess pulmonary vein isolation. The concomitant coronary or valve procedure(s) was/were then performed.

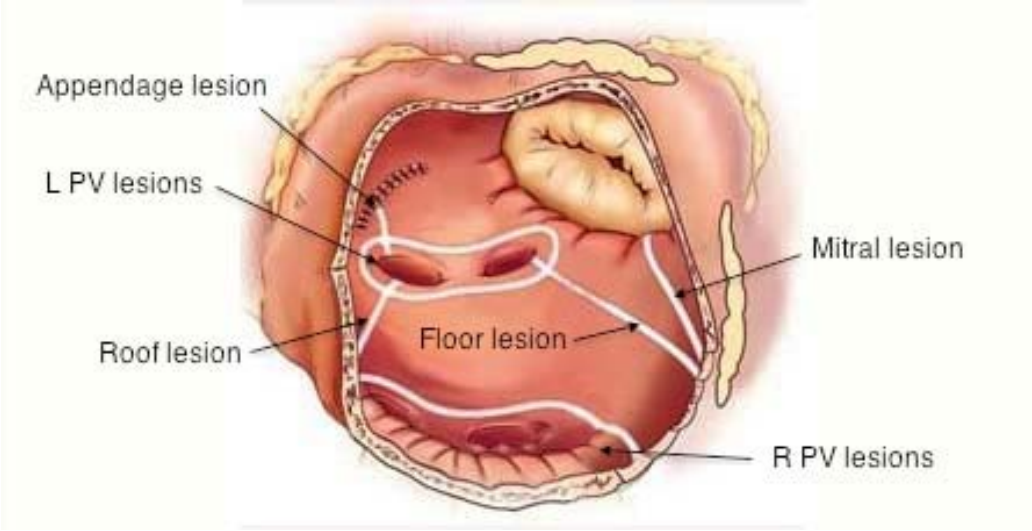

Figure 4. Left Atrial Lesions, Cox Maze IV Procedure
Modified from http://www.surgery.wustl.edu/Surgery_M.aspx?id=1570&menu_id=392

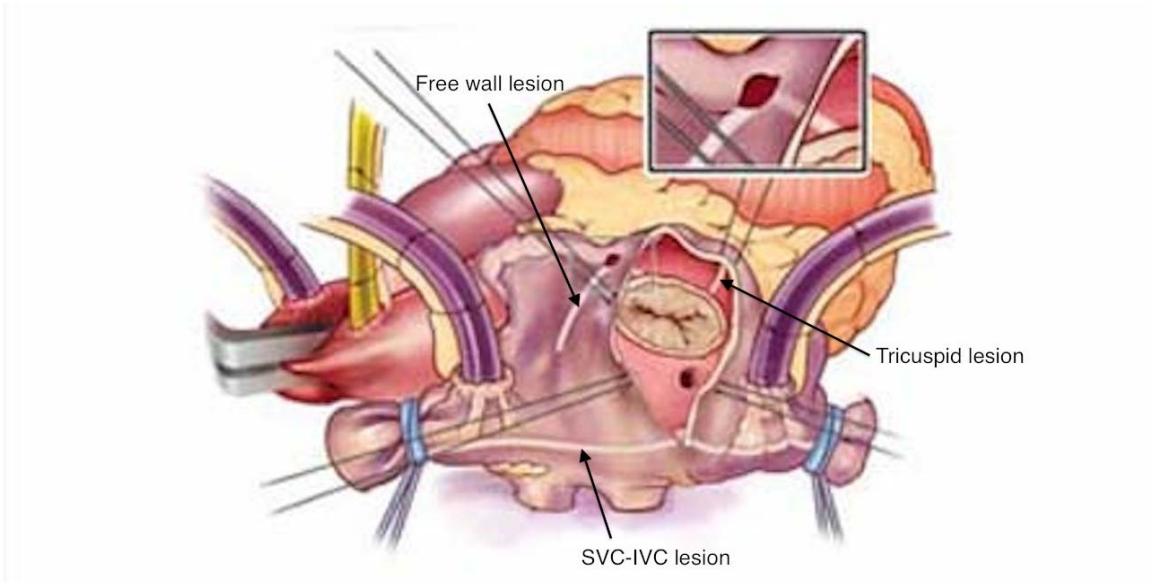

Figure 5.Right atrial lesions, Cox Maze IV Procedure
Modified from http://www.surgery.wustl.edu/Surgery_M.aspx?id=1570&menu_id=392

As shown in the following table, per the investigational plan, the AtriCure Synergy Ablation System alone (i.e. the Synergy Ablation Clamp) was to be used for 6 of the 9 lesions. For the remaining 3 lesions, another modality (the AtriCure Bipolar Pen or a cryo-surgical method) was allowed to perform or complete the lesion. The concomitant surgical procedure (CABG, mitral valve, aortic valve, etc.) was then performed.

Lesion	Device Recommended
Right and Left Pulmonary Vein	Synergy Ablation Clamp only
Roof Line	Synergy Ablation Clamp only
Floor Line	Synergy Ablation Clamp only
Mitral Valve Connecting	Initiated with Synergy Ablation Clamp, completed with AtriCure Transpolar Pen or cryo-surgical device
Left Atrial Appendage to Pulmonary Vein	Synergy Ablation Clamp only
Right Tricuspid Valve	Synergy Ablation Clamp, AtriCure Transpolar Pen, or a cryo-surgical device
SVC to IVC	Synergy Ablation Clamp only
Free Wall Appendage	Synergy Ablation Clamp only
Right Atrial Appendage to Tricuspid Annulus	Synergy Ablation Clamp, AtriCure Transpolar Pen or cryo-surgical device
Septal Lesion (optional)	Any technique

Table 3. Lesion Set Protocol Requirements

FDA Commentary: FDA believes that the surgical instructions as specified in the protocol are important for informing the instructions for use for the device. Non-compliance with these instructions (i.e. using cryoablation or other modalities to create lesions specified to be performed with the Synergy Ablation Clamp) challenges interpretation of study results and writing of instructions for use. This is discussed in more detail below under Section 7.9.3.

After surgery, subjects were placed on either a Class I or Class III anti-arrhythmic drug (AAD) immediately. They received anti-coagulation according to the clinician's preference and clinical indications. They were followed through discharge, at 30 days, 3 months, 6 months, 12 months, 18 months, 2 years and annually for five years thereafter. Clinic visits were required at 3- and 6-months; telephone contact could be performed at other times. Assessments included a targeted history and physical exam, as well as a recording of current medications and an ECG. At two months, an optional clinical assessment was encouraged as a means of evaluating the subject's AF status

while on AADs. AADs were to be discontinued at the 3-month visit. At each clinic visit, subjects were evaluated for safety.

Subjects were to be weaned off their AADs at least five half-lives before the 6-month assessment. This meant 4 weeks for Class I agents or sotalol, and 12 weeks for amiodarone. Cardioversions were permitted up to the 6-month assessment and recommended by the protocol at any visit at which a subject was in AF or atrial flutter, if tolerated.

7 CLINICAL STUDY RESULTS

This section discusses the results of the ABLATE clinical trial. It begins by summarizing patient accountability and site enrollment for the ABLATE clinical study. The primary safety and effectiveness analyses are presented, and additional pre-specified and post hoc data are also discussed.

7.1 Subject Accountability

A total of 56 subjects presented for surgery. One subject who presented for surgery was noted by intraoperative TEE to have a left atrial size that did not meet the eligibility criteria (observed LA size > 8 cm diameter) and therefore was not treated with the investigational system. Fifty-five subjects from 9 US sites were treated.

The analysis population for the primary effectiveness endpoint included subjects that were evaluable for the primary effectiveness endpoint ("completers"). This population excluded five (5) subjects: There were 2 post operative deaths (considered safety endpoint events), 2 deaths beyond three months but less than six months (not considered safety endpoint events as they occurred beyond 30 days), and 1 subject who withdrew from the study at the 30-day visit. Therefore, the treated population for the primary effectiveness assessment was initially 50 subjects. All non-completers were classified as having persistent or longstanding persistent AF. Figure 6 below details subject accountability through two years.

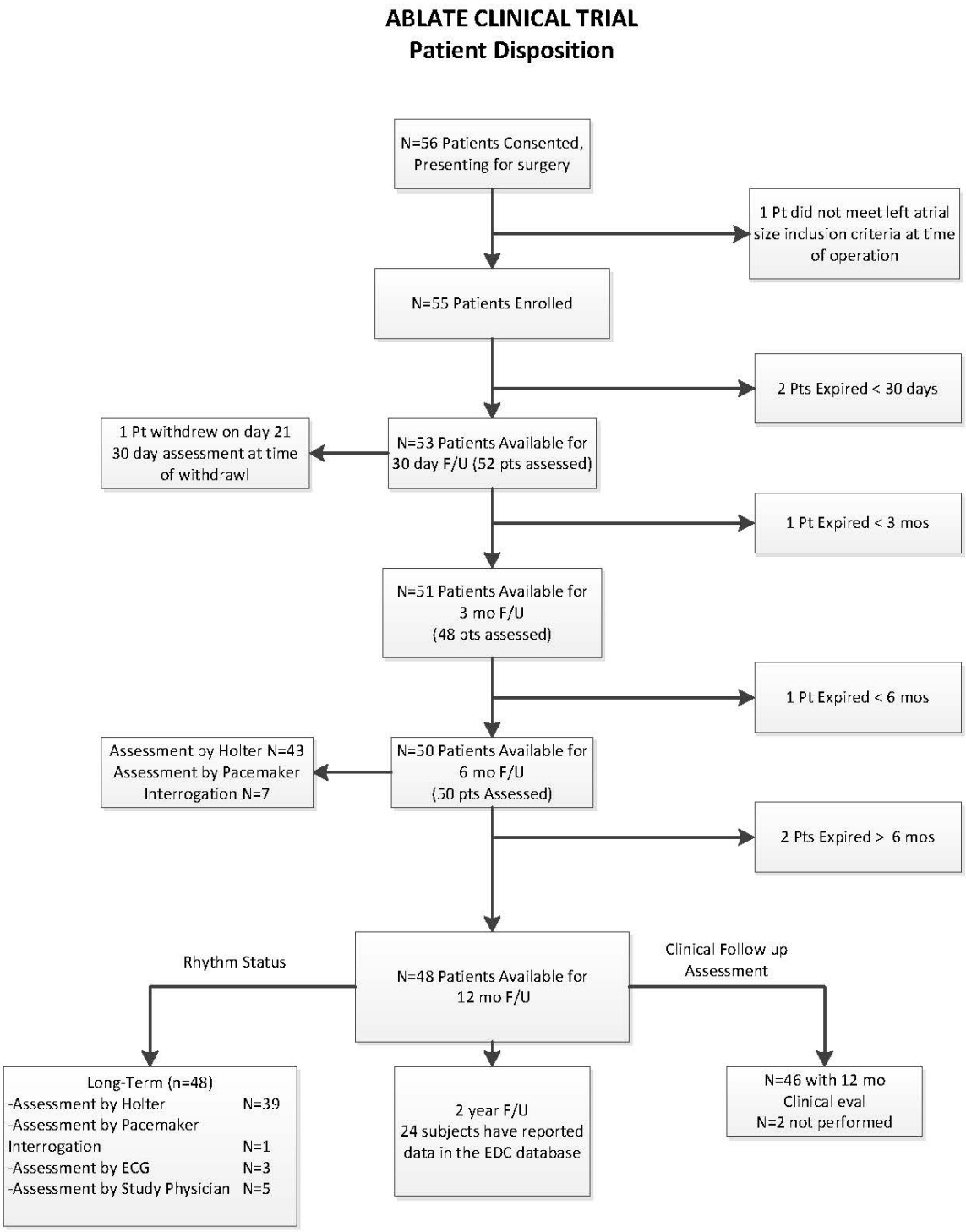

Figure 6. Subject accounting in the ABLATE clinical study.

Note that upon re-classification by outside expert review (see discussion below), 4 subjects were classified as having paroxysmal AF, leaving a final *non-paroxysmal* population of 46 to be evaluated for effectiveness. The following table presents the distribution of subjects enrolled in the ABLATE clinical study by AF classification.

AF Classification	Number of Subjects Enrolled
Paroxysmal	4
Persistent	22
Longstanding persistent	29

Table 4. Number of subjects in ABLATE by AF Classification

7.2 Subject Demographics

The subject population is typical for patients undergoing cardiac surgery. The average duration of AF was about 5 years but there was wide variation. Most subjects had AF for longer than one year, and the left atrium was mildly dilated. Subject demographics are presented in the table below for all treated subjects.

	Mean	Range
Age (years)	70.5 ± 9.3	45 – 88
Male	58.2%	
Duration of AF (months)	61.2 ± 49.5	1.78 – 188.4
AF longer than 1 year	85.5%	
Ejection fraction (%)	50.0 ± 10.3	20.0 – 77.0
LA size (cm)	5.9 ± 1.0	3.9 – 7.7

Table 5. Key ABLATE Subject Demographics

7.3 Procedures Performed

Concomitant procedures were performed on all 55 subjects who were treated with the device. As detailed in the table below, valve surgery was performed in the majority of subjects, either alone (56.4%) or in combination with coronary artery bypass grafting (25.5%). Isolated coronary bypass made up an appreciable minority of procedures (18.2%). Mitral surgery in any form was undertaken in 54.5% of subjects.

Concomitant Procedure Performed	Percentage
CABG only	18.2%
Valve Surgery	40.0%
Mitral Valve Repair/Replacement	18.2%
Aortic Valve Repair/Replacement	21.8%
Double Valve Surgery	16.4%
Aortic & Mitral	7.3%
Mitral & Tricuspid	9.1%
CABG and Valve Surgery	16.4%
CABG + Mitral Valve Repair/Replacement	10.9%
CABG + Aortic Valve Repair/Replacement	5.5%
CABG + Double Valve Surgery	9.1%
Aortic & Mitral	5.5%
Mitral & Tricuspid	3.6%

Table 6. Concomitant procedures performed

FDA commentary: The wide variety of procedures performed confirms that patients who present for cardiac surgery with atrial fibrillation very often have mitral valve disease. However, almost one in five subjects underwent ablation during isolated coronary artery bypass grafting, suggesting that the device will also be widely used in this population.

7.4 Interim Analysis

7.4.1 Treated Population

The Sponsor conducted the first interim look when 55 patients had been enrolled and all had provided the 30-day safety outcome. The pre-specified safety performance goal was met; therefore, the predictive probability of meeting the safety endpoint with the current sample size was 100%.

As discussed above in section 7.1, there were 50 patients for the effectiveness analysis, and there were 24 effectiveness successes out of 29 patients providing 6-month data. After calculation, the predictive probability of meeting the effectiveness endpoint with the current sample size was 98.8%, which exceeded the stopping boundary. Thus the trial accrual was stopped per the pre-specified stopping rules.

7.4.2 Non-Paroxysmal population

As discussed above, 4 subjects were excluded from the study upon retrospective rhythm re-classification, as they had *paroxysmal* AF. A retrospective interim analysis was conducted by the Sponsor at the request of FDA for persistent and long-standing persistent (i.e. non-paroxysmal) patients. The first possible interim analysis point was predefined as the point at which 50 subjects were enrolled with a minimum of 20

subjects through six months follow-up. As such, the first interim analysis was conducted at the point where the 50th non-paroxysmal subject was enrolled in the trial.

At this point in time, there were 48 non-paroxysmal subjects with 30-day safety outcome assessments; two subjects had not yet reached the 30-day time point. All of the safety events in the ABLATE study (5 MAEs) occurred in non-paroxysmal subjects. The predictive probability of meeting the safety endpoint with the current sample size was 0%. This is because at most 4 safety events can occur while still meeting the performance goal for the safety endpoint with 50 subjects .The predictive probability of meeting the safety endpoint at the maximum sample size of 100 patients is 68.2%.

As discussed above, 5 patients (4 deaths, 1 withdrawn) were excluded from the effectiveness analysis. Out of the 45 remaining patients, there were 13 subjects through three months of follow-up and 27 subjects through six months follow-up. The predictive probability of meeting the effectiveness endpoint with the current sample size was 55%, and the predictive probability of meeting the effectiveness endpoint at the maximum sample size of 100 patients is 82.6%.

Therefore, had only non-paroxysmal subjects been included, the criterion for stopping enrollment would not have been met, and enrollment in the trial would have continued. The Tables below summarize the interim analysis results.

Test for Stopping Enrollment (Current Sample)			
	Predictive probability of meeting Effectiveness Endpoint	**Predictive Probability of meeting Safety Endpoint**	**Predictive Probability of a win (Stopping Boundary = 0.9)**
Treated population	0.988	1.0	0.988 Stopping Criterion MET
Non-paroxysmal population	0.55	0.000	0.000 Stopping Criterion NOT MET

Test for Futility (Max N)			
	Predictive probability of meeting Effectiveness Endpoint	**Predictive Probability of meeting Safety Endpoint**	**Predictive Probability of a win (Stopping Boundary = 0.05)**
Treated population	0.992	0.846	0.838 Stopping Criterion NOT MET
Non-paroxysmal population	0.826	0.682	0.564 Stopping Criterion NOT MET

Table 7. Interim Analysis Results for Test for Stopping Enrollment (upper) and for Test for Futility (lower)

FDA Commentary: As discussed above, the Sponsor is targeting a population of patients with non-paroxysmal AF. Evaluating only non-paroxysmal AF patients reduces the already-small ABLATE data set by 4. Not only does this have possible implications for interpretation of data in the final analyses, but also for the course of study progress. As demonstrated in this section on Interim Analysis, had the Sponsor considered only non-paroxysmal subjects at the time of the Interim Analysis, enrollment would have continued, perhaps yielding a larger analysis cohort.

7.5 Primary Safety Endpoint Results

7.5.1 Treated Population

The primary safety endpoint was evaluated on an intention-to-treat basis for all 55 subjects enrolled and treated. The composite endpoint included death (within 30 days or beyond 30 days if considered device related), bleeding > 2 units of RBCs with reoperation, stroke or TIA, or MI. There were five safety failures: two deaths, two excessive bleeds and one stroke. Only one of the 5 MAEs, a death, was attributed to the Maze procedure by the independent physician adjudicator. None of the MAEs was found to be device related. The safety results are detailed in the table below, along with the Bayesian 95% credible intervals (BCI) for the composite.

Primary Safety Endpoint	% (n/N)	BCI
Composite MAE within 30 days	9.1% (5/55)	(0.00, 0.179)
Death	3.6% (2/55)	
<=30 days	3.6% (2/55)	
>30 days, procedure related	0.0% (0/55)	
Stroke/TIA	1.8% (1/55)	
Stroke (with significant permanent disability)	1.8% (1/55)	
TIA	0.0% (0/55)	
MI	0.0% (0/55)	
Excessive Bleeding (>2 units blood and surgical intervention)	3.6% (2/55)	

Table 8. Primary Safety Endpoint for Treated Population

The pre-specified performance goal for the primary safety endpoint was a composite event rate of <18.95%. The posterior probability that the safety rate is less than 0.1895 is

$$\mathbf{Pr(}q_T \mathbf{< 0.1895 \mid Trial\ Results) = 0.967} > 0.95.$$

This posterior probability exceeds 95%, the a priori defined threshold of safety success. The upper bound of the BCI (17.9%) is below the threshold of 18.95% established for safety success. Thus, the primary safety endpoint is met.

The following figure shows the posterior distribution of q_T, the composite MAE rate within 30 days for the treated population.

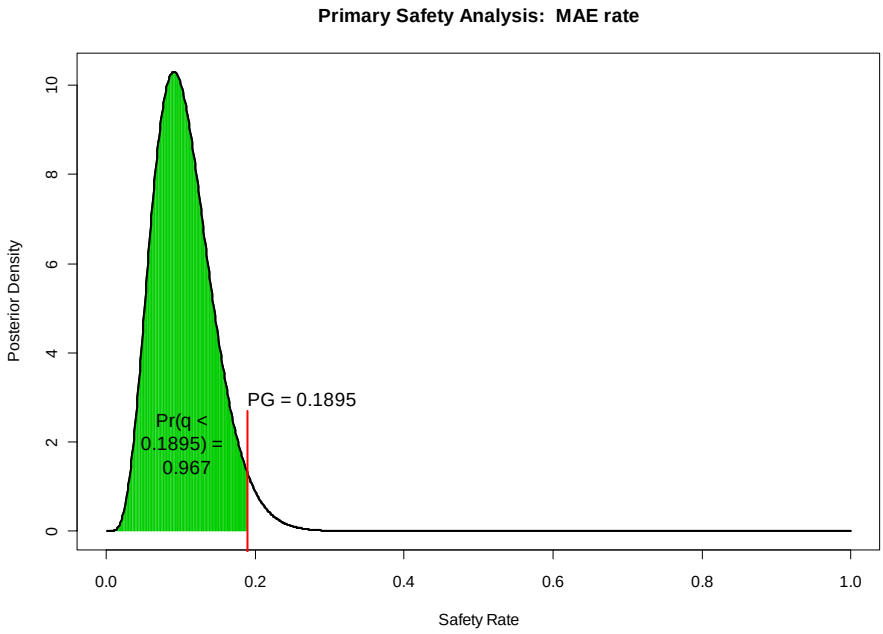

Figure 7. Primary Safety Analysis: Posterior Distribution of q_T for All Treated Subjects

FDA commentary: There are several concerns with these data. First, although the safety endpoint was met successfully, it was with no margin. That is, if one more event had occurred (6 MAEs instead of 5), the posterior probability that the safety rate is <0.1895 would be 0.926, which is less than the 95% threshold. This is illustrated in Figure 8.

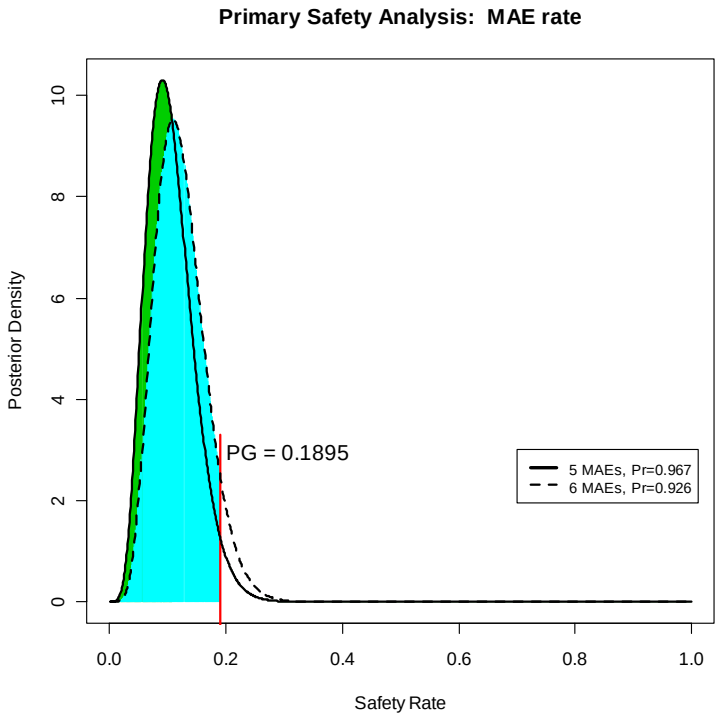

Figure 8. Posterior Distribution of qT for All Treated Subjects with 5 MAEs (observed) and 6 MAEs (projected)

Second, inclusion of paroxysmal AF subjects in a safety calculation may bias the results toward success, as paroxysmal patients tend to be healthier than those with more advanced forms of AF and would be expected to suffer fewer adverse events.

In an attempt to understand better device safety in a "non-paroxysmal" population, FDA asked for independent corroborative data. This was obtained through the Sponsor's ABLATE AF registry, a previous IDE study (RESTORE), and through two institutional databases (Washington University and Baylor-Plano). The results from these sources are presented separately below in section 8.

7.5.2 Non-Paroxysmal Population

The following table provides the primary safety results for only subjects categorized as having persistent or longstanding persistent AF.

Primary Safety Endpoint	% (n/N)	BCI
Composite MAE within 30 days	9.8% (5/51)	(0.00, 0.192)
Death	3.9% (2/51)	
<=30 days	3.9% (2/51)	
>30 days, procedure related	0.0% (0/51)	

Primary Safety Endpoint	% (n/N)	BCI
Stroke/TIA	2.0% (1/51)	
Stroke (with significant permanent disability)	2.0% (1/51)	
TIA	0.0% (0/51)	
MI	0.0% (0/51)	
Excessive Bleeding (>2 units blood and surgical intervention)	3.9% (2/51)	

Table 9. Primary Safety Endpoint for Non-Paroxysmal Population

The posterior distribution for the safety rate becomes qT | Trial Results ~ Beta(1+5, 1+46) = Beta(6,47). The posterior probability the safety rate is less than 0.1895 is

$$\mathbf{Pr(q_T < 0.1895 \mid Trial\ Results) = 0.946} < 0.95.$$

Under these conditions, the study would not meet the a priori defined threshold of safety success, which is 95%.

The following figure shows the posterior distribution of q_T, the composite MAE rate within 30 days for the non-paroxysmal population.

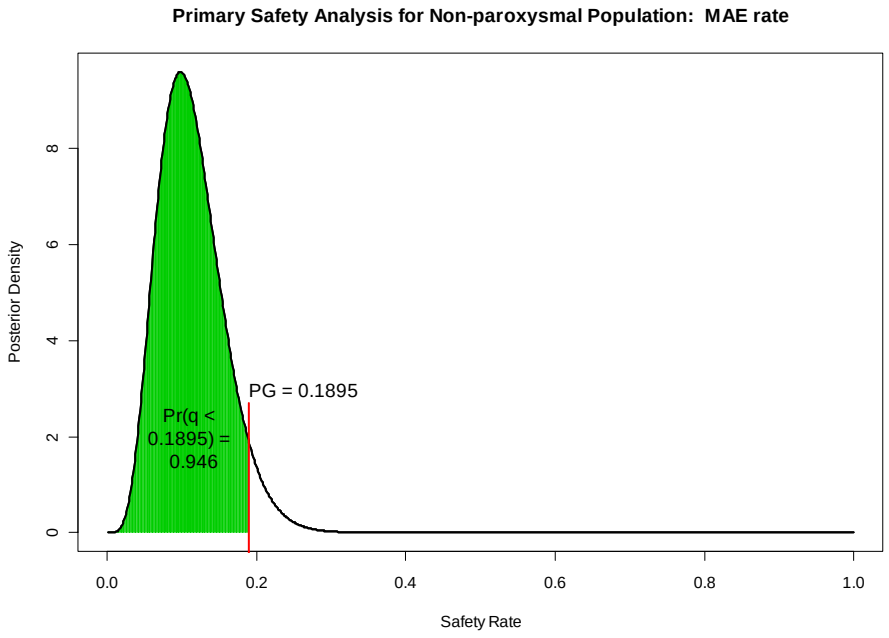

Figure 9. Primary Safety Analysis: Posterior Distribution of q_T for Non-Paroxysmal Subjects

FDA Commentary: This recalculation, using only the 51 "non-paroxysmal" subjects, shows that the trial just fails to meet the safety performance goal (MAE rate = 5/51 = 9.8%, BCI = 0.0% – 19.2%). This supports the contention that the inclusion of "healthier", paroxysmal AF subjects biases the study toward an overall safety success.

7.6 Primary Effectiveness Endpoint Results

7.6.1 Treated Population

The following table provides the primary effectiveness results for all 50 treated, evaluable patients enrolled in the study. The primary effectiveness endpoint was defined as freedom from AF at 6-months, off AADs. Freedom from AF was defined as no episode of AF lasting longer than 5 minutes on 24-hour Holter. The pre-defined performance goal for the primary effectiveness endpoint was 60%.

Primary Effectiveness Endpoint	% (n/N)	BCI
Primary Success at 6 months*	74.0% (37/50)	(0.604, 1.00)
Failure by AAD	10.0% (5/50)	
Failure by Rhythm	16.0% (8/50)	

Table 10. Primary Effectiveness Endpoint for Treated Population

The posterior probability that the primary effectiveness rate exceeds 0.60 is

$$\mathbf{Pr(p_T > 0.60 \mid Trial\ Results) = 0.978} > 0.975$$

This posterior probability exceeds 97.5%, the a priori defined threshold of effectiveness success. The lower bound of the BCI is above the threshold of 60% established for effectiveness success. On these grounds, the trial has successfully met its primary effectiveness endpoint hypothesis.

The following figure shows the posterior distribution of p_T, AF-free and off AADs at 6 months for the treated population.

* One subject was weaned from AADs after the 3-month period dictated by the study protocol. A Holter monitor was performed *after the drug washout period* and used retrospectively for assessment of the primary effectiveness endpoint.

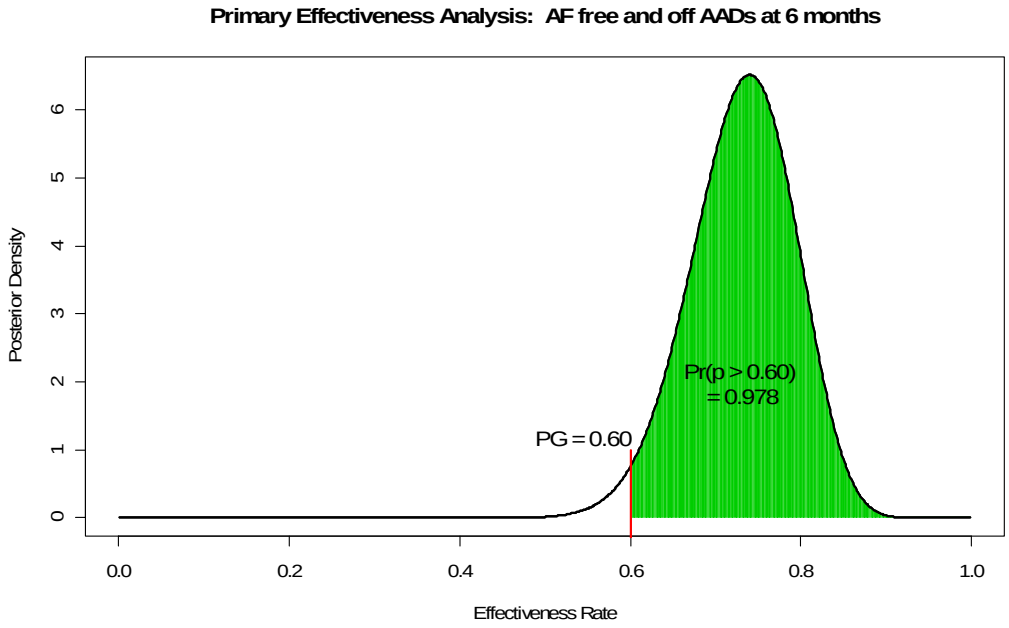

Table 11. Primary Effectiveness Analysis: Posterior Distribution of p_T for All Treated Subjects

FDA Commentary: This presented analysis is a complete case analysis, which excludes 5 subjects without 6-month effectiveness data (4 deaths, and 1 withdrawn), and ignores the effect of missing data.

A tipping point sensitivity analysis was conducted to determine the success rate required for the non-completers in order to meet the pre-specified performance goal. This analysis demonstrates that at least 4 out of the 5 unobservable subjects must be effectiveness successes in order to meet the pre-specified performance goal. The results of this analysis are presented in the table and figure below.

Successes out of 5 unobservable patients	Total Successes out of 55	Pr(p_T > 0.60 | Trial results)	1-sided 97.5% BCI
0	37	0.857	(0.540,1.00)
1	38	0.911	(0.559,1.00)
2	39	0.948	(0.578,1.00)
3	40	0.972	(0.597,1.00)
4	**41**	**0.986**	**(0.616,1.00)**
5	**42**	**0.994**	**(0.636,1.00)**

Table 12. Tipping Point Analysis

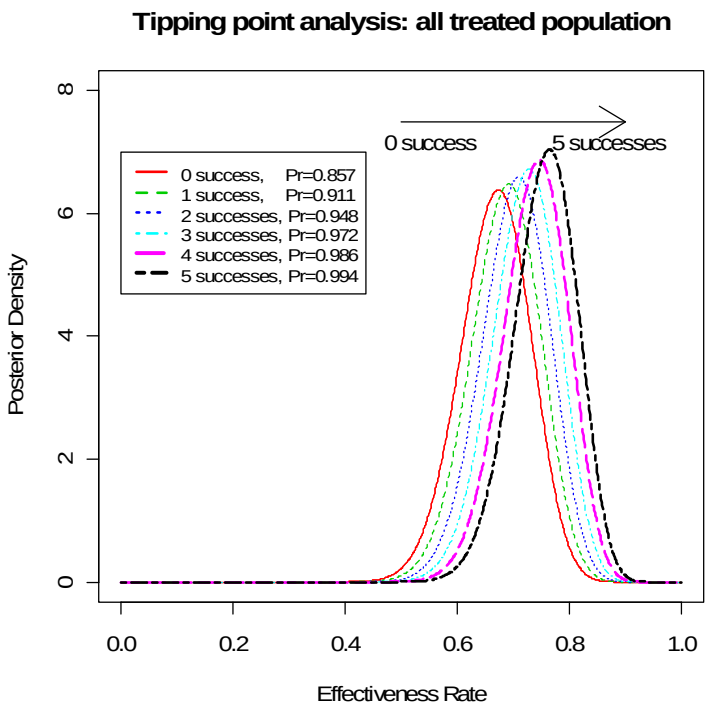

Figure 10. Tipping Point Analysis for the Treated Population. This figure shows how the posterior distribution for p_T shifts with increasing numbers of successes such that with 4 successes, $Pr(p_T > 0.60 \mid \text{Trial results}) > 0.975$.

7.6.2 Non-Paroxysmal Population

The following table provides the effectiveness results for all patients categorized as having persistent or longstanding persistent AF, excluding those with paroxysmal AF.

Primary Effectiveness Endpoint	% (n/N)	BCI
Primary Success at 6 months	73.9% (34/46)	(0.597, 1.00)
Failure by AAD	8.7% (4/46)	
Failure by Rhythm	17.4% (8/46)	

Table 13. Primary Effectiveness Endpoint for Non-Paroxysmal Population

The posterior probability that the effectiveness rate exceeds 0.60 is

$$\mathbf{Pr(p_T > 0.60 \mid Trial\ Results) = 0.972} < 0.975.$$

This result is less than the a priori defined threshold of effectiveness success, 97.5%, and the lower bound of the BCI is less than 60%. Therefore, when considering only the non-paroxysmal population, the trial does not successfully meet its primary effectiveness endpoint hypothesis by a small amount.

The following figure shows the posterior distribution of p_T, AF-free and off AADs at 6 months for the non-paroxysmal population.

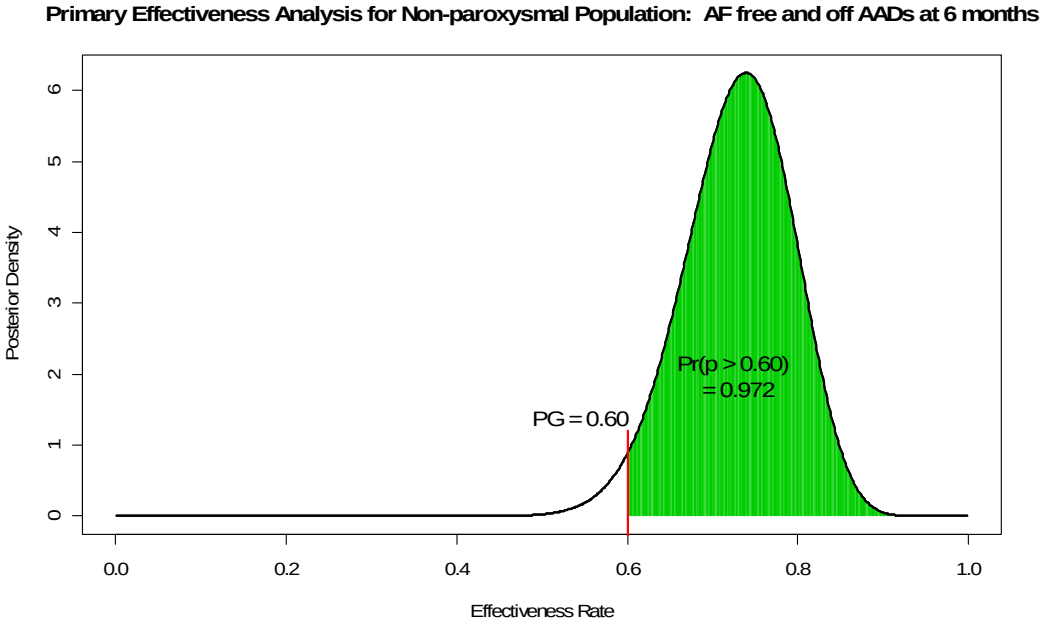

Figure 11. Primary Effectiveness Analysis: Posterior Distribution of p_T for Non-Paroxysmal Subjects

FDA Commentary: As with the safety evaluation, re-calculation of the effectiveness data considering only those subjects with non-paroxysmal AF shows that the trial fails to show device effectiveness per the pre-specified performance criteria by a small amount.

Also, as noted above for the Treated population, this presented analysis is a complete case analysis, which excludes 5 subjects without 6-month effectiveness data (4 deaths, and 1 withdrawn), and ignores the effect of missing data. A tipping point analysis demonstrates that at least 4 out of the 5 unobservable subjects (80%) must be effectiveness successes in order to meet the pre-specified performance goal.

Successes out of 5 unobservable patients	Total successes out of 51	Pr(p_T > 0.60 | Trial results)	1-sided 97.5% BCI
0	34	0.825	(0.529,1.00)
1	35	0.889	(0.549,1.00)
2	36	0.935	(0.569,1.00)
3	37	0.965	(0.590,1.00)
4	**38**	**0.983**	**(0.611,1.00)**
5	**39**	**0.992**	**(0.632,1.00)**

Table 14. Tipping Point Analysis

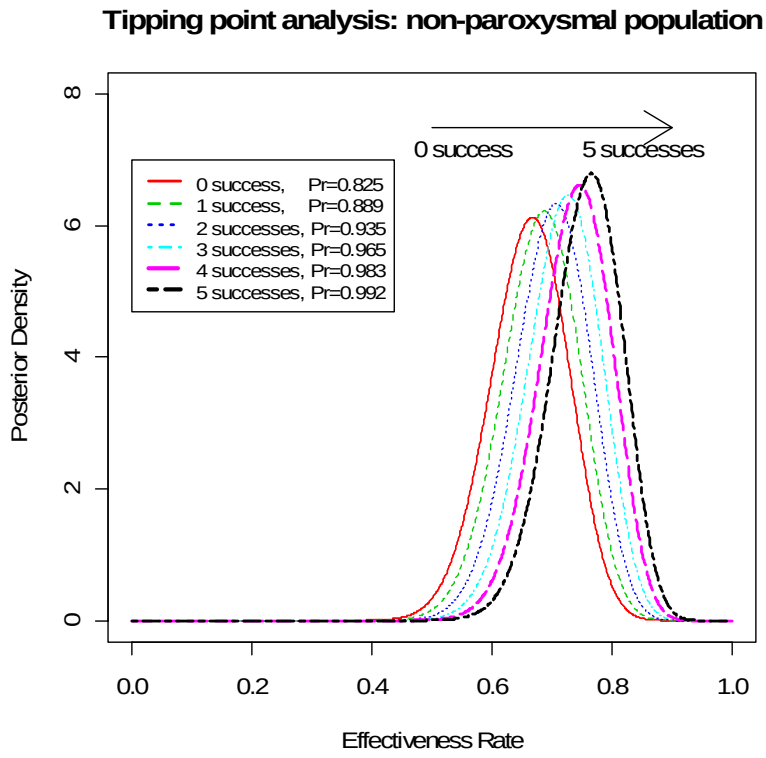

Figure 12. Tipping Point Analysis for the Non-Paroxysmal Population. This figure shows how the posterior distribution for p_T shifts with increasing numbers of successes such that with 4 successes, $Pr(p_T > 0.60 \mid \text{Trial results}) > 0.975$.

7.7 Secondary Endpoints

7.7.1 Secondary Safety Endpoints

The secondary safety endpoints of composite 6-month major adverse event rate and overall 6-month adverse event rate are given in the following table for the Treated and Non-Paroxysmal populations.

Secondary Safety Endpoints	Treated % (n/N)	Non-Paroxysmal % (n/N)
MAE through 6 months	10.9% (6/55)	11.8% (6/51)
Death	7.3% (4/55)	7.8% (4/51)
Stroke (with significant permanent disability)	1.8% (1/55)	2.0% (1/51)
TIA	0.0% (0/55)	0.0% (0/51)
MI	0.0% (0/55)	0.0% (0/51)
Excessive Bleeding (>2 units blood and surgical intervention)	3.6% (2/55)	3.9% (2/51)
Any Adverse Event through 6 months	90.9% (50/55)	94.1% (48/51)
Any Serious Event	74.5% (41/55)	76.5% (39/51)
Any Device Related Event	0.0% (0/55)	0.0% (0/51)
Any AF-Procedure Related Event	14.5% (8/55)	15.6% (8/51)
Any Serious Device Related Event	0.0% (0/55)	0.0% (0/51)
Any Serious AF-Procedure Related Event	12.7% (7/55)	13.7% (7/51)

Table 15. Secondary Safety Endpoints for Treated and Non-Paroxysmal Patients

7.7.2 Secondary Effectiveness Endpoints

The secondary endpoints below are presented for both the Treated and Non-Paroxysmal populations.

7.7.2.1 Freedom from AF independent of AADs and AF Burden at 6 Months

Freedom from AF, whether on or off AADs, is shown in the table below. The table also shows the AF burden in a 24-hour period measured either with a 24-hour Holter (44 Treated, 40 Non-Paroxysmal) or pacemaker interrogation (6 Treated, 6 Non-Paroxysmal).

Secondary Effectiveness Endpoint	Treated % (n/N)	Non-Paroxysmal % (n/N)
Free of AF, Regardless of AADs*	84.0% (42/50)	82.6% (38/46)
AF Burden		
= 0 min	82.0% (41/50)	82.6% (38/46)
<= 5 min	2.0% (1/50)	0% (0/46)
> 5 min - 1 hr	2.0% (1/50)	0% (1/46)
> 1 hr	14.0% (7/50)	15.2% (7/46)

Table 16. Secondary Effectiveness Endpoints for Treated and Non-Paroxysmal Subjects

* Using the definition of the 2006 Guidelines: "AF free" = no episodes > 5 minutes

7.7.2.2 Acute Pulmonary Vein Isolation

Exit block was assessed by pacing from the pulmonary veins after ablation. This was technically possible in 23 subjects. Complete block was demonstrated in all of them.

Secondary Effectiveness Endpoint	% (n/N)
Both Right & Left Pulmonary Vein Isolation	
Isolation Confirmed (Of 23 evaluable subjects)	100.0% (23/23)

Table 17. Pulmonary Vein Isolation

7.8 Key Additional Analyses Provided by the Sponsor

7.8.1 Permanent Pacemaker Implantation

Ablation may have an effect on the cardiac conduction system. Damage to the sinoatrial and/or atrioventricular nodes may result in pacemaker implantation after treatment. Seven of the 55 subjects who presented for treatment already had pacemakers implanted. In the remaining 48 subjects, 12 pacemakers were implanted within 30-days after ablation (25%): 4 for A-V nodal dysfunction, and 8 for sinus node dysfunction. Four more pacemakers were implanted later, bringing the cumulative total to 33%. All of the later implants were for sinus node dysfunction, and all occurred between 30-days and 6-months. This is detailed in the table below.

	In Hospital	Cumulative to 30 days	Cumulative to 6 months	Cumulative to 12 months
	% [n/N]	% [n/N]	% [n/N]	% [n/N]
Permanent Pacemaker Implantation	25.0% (12/48)	25.0% (12/48)	33.3% (16/48)	33.3% (16/48)
AV node dysfunction	8.3% (4/48)	8.3% (4/48)	8.3% (4/48)	8.3% (4/48)
Sinus node dysfunction	16.7% (8/48)	16.7% (8/48)	25.0% (12/48)	25.0% (12/48)

Table 18. Rates of Pacemaker Implantation

FDA's commentary: Although not formally studied in controlled trials, recent meta-analyses of the literature on surgical ablation for AF reveal the pacemaker implantation rate after treatment to be between 0% and 21%, with a weighted mean of 4.9% for alternative energy sources and 5.8% for the Cox Maze III "cut & sew" technique.[*] There was no significant difference between the two methods. Although not formally tested, the observed rate of pacemaker implantation in ABLATE subjects is higher than the highest rate cited in these reviews for unclear reasons.

[*] Khargi et al., 2007, Herzschrittmacherther Elektrophysiol, 18, 68-76; Khargi et al., 2005, Eur J Cardiothorac Surg, 27, 258-65

7.8.2 Device- and Ablation-Procedure Related Adverse Events

The following table presents the adverse events related to the device and AF ablation procedure. All of these events occurred prior to discharge for the index procedure. There were no adverse events adjudicated as related to the device. Of the 8 adverse events related to the AF procedure, 7 were serious. In addition to those listed in the table, one serious adverse event (ischemia requiring bypass) was attributed to the ancillary AtriCure pen used to complete the lesion to the tricuspid annulus.

Parameter	# of Evts	% (n/N) of Pts with Event
Device Related Adverse Event	**0**	**0.0% (0/55)**
AF Procedure Related Adverse Event	**8**	**14.5% (8/55)**
Cardiac disorders	**6**	**10.9% (6/55)**
Atrial rupture	**1**	**1.8% (1/55)**
Atrioventricular block	**1**	**1.8% (1/55)**
Atrioventricular block first degree	**1**	**1.8% (1/55)**
Atrioventricular block second degree	**1**	**1.8% (1/55)**
Bradycardia	**2**	**3.6% (2/55)**
Injury, poisoning and procedural complications	**2**	**3.6% (2/55)**
Vena cava injury	**1**	**1.8% (1/55)**
Venous injury	**1**	**1.8% (1/55)**

Table 19. Adjudicated Device- and AF Procedure-Related Adverse Events

FDA Commentary: Although not a primary endpoint, FDA believes that device- and AF procedure-related adverse events are important information to track. As such, as noted below, FDA recommends that the safety endpoint of any post-approval study be built around these types of events rather than the MAEs specified above, which are largely due to the concomitant procedure.

7.8.3 Freedom from AF at 12 or More Months

Late follow-up was obtained for subjects at least one year after treatment in order to assess effectiveness over time. The additional endpoints to be studied were: (1) Freedom from AF, off AADs; (2) Freedom from AF, regardless of AADs; and (3) AF burden. The median follow-up was 658 days (range 365 - 952 days). The data shown below are divided according to the populations of interest; the exact number of subjects varies because of the retrospective collection without all subjects being available.

	Treated	Non-Paroxysmal
Additional Effectiveness Endpoints	**% [n/N]**	**% [n/N]**
Free of AF* at 12+ months	75.0% (36/48)	73.3% (33/45)
Free of AF and off AAD at 12+ months	62.5% (30/48)	62.2% (28/45)
AF Burden (initial 24 hrs or >24 - 48 hrs) at 12+ months		
= 0 min	77.5% (31/40)	76.3% (29/38)
<= 5 min	0.0% (0/40)	0.0% (0/38)
> 5 min - 1 hr	0.0% (0/40)	0.0% (0/38)
> 1 hr	22.5% (9/40)	23.7% (9/38)

Table 20. Additional Effectiveness Endpoints for Treated and Non-Paroxysmal Subjects

FDA's commentary: Beyond 12 months, there are no subjects with "short duration" episodes of AF; the subject is either free of AF or in AF continuously. There also appears to be a fall-off in freedom from AF over time: At 6 months, 74.0% of subjects were free of AF, off AADs, whereas at 12 months there were only 62.5%. Disregarding AAD usage, 84.0% were free of AF at 6 months compared to 75.0% at 12 months. A much slower fall-off has been shown after the Cox-Maze III (cut & sew) procedure, typically over 5 – 10 years.†

7.9 Ancillary Analyses

During the PMA review process, several issues arose. For each section below, FDA requests Panel input to assist in further evaluation. FDA acknowledges that the ancillary analyses presented here are post-hoc. However, FDA believes that these are important considerations in evaluating whether the data provide a reasonable assurance of safety and effectiveness of the AtriCure Synergy Ablation System for the desired indication.

7.9.1 Inadequate Drug Washout at 6 Months

In the results reported above, 4 subjects had their primary effectiveness endpoint status imputed because they could not be evaluated at 6 months.‡ For imputation the Sponsor applied this algorithm: The 6-month Holter data would be considered a success if and only if both the 2nd and 3rd Holter recordings showed freedom from AF, off AADs.§ Accordingly, 1 subject was reported as a primary effectiveness success and 3 were reported as failures. However, data for this subject was indeed available in real time; the subject was free of AF but *not outside the drug washout window* when the 6-month Holter recording was performed.

* Using the definition of the 2006 Guidelines: "AF free" = no episodes > 5 minutes
† Gaynor et al. 2005, Journal of Thoracic and Cardiovascular Surgery.129, 104-111.
‡ More specifically, three subjects were not through the washout period and one subject had an uninterpretable Holter recording.
§ The 2nd Holter recordings were performed when the washout period was completed, between 368 and 630 days. The 3rd Holter recordings were performed during efforts to obtain long-term follow-up data from ABLATE study patients, between 616 and 851 days.

It is FDA's position that, according to the study definitions of success, any subject who is still within the AAD washout period cannot qualify as being "off AADs". This means that the subject imputed to be a success should be counted as a failure. FDA is not aware of any scientific evidence demonstrating that AF behaves in a "monotonic" fashion after an ablation procedure; that is, once a patient is free of AF they remain free of it, or when a patient relapses into AF they always stay in AF. This means that later rhythm observations can not reflect previous rhythm behavior. FDA therefore maintains that the imputation algorithm used above is invalid, and if the subject under discussion (a non-paroxysmal subject) were to be considered a failure as defined in the study protocol, the primary effectiveness results would now be:

	Treated	**Non-Paroxysmal**
Primary Effectiveness Endpoint	**% (n/N) [97.5% BCI]**	**% (n/N) [97.5% BCI]**
Primary Effectiveness Success at 6 months, *beyond AAD washout period*	72.0% (36/50) [0.583, 1.00]	71.7% (33/46) [0.574, 1.00]

Table 21. Primary Effectiveness Endpoint Considering Late AAD Washout

The posterior distributions of p_T, AF-free and off AADs at 6 months considering late AAD washout are shown in Figure 13 in section 7.9.5 below.

7.9.2 Cardioversions Performed

According to the study protocol, DC cardioversions were permitted at any time during the follow-up period, up to the 6-month assessment. The table below indicates which subjects had cardioversion (CV) between treatment and 6 months, and how many days elapsed between the CV and the assessment of the primary effectiveness endpoint.

Effectiveness Status at 6 months	**AF Class**	**Number of Subjects Having CV during 6-Mo Follow-up**	**Number of subjects having CV after 3 months (days between CV and 6 Mo Eval)**
AF Free off AADs	PER	3	0
	LSP	3	**1 (77)**
AF Free on AADs	PER	1	0
	LSP	1	**1 (9)**
in AF	PER	1	0
	LSP	3	**2 (29, 61)**

Table 22. Patients with Cardioversion Close to the Primary Effectiveness Evaluation

Six subjects classified as primary effectiveness successes underwent cardioversion prior to the 6 month follow-up assessment, all at least 77 days prior to the primary effectiveness assessment. The other 6 subjects, who were all classified as primary effectiveness failures, underwent cardioversion between 9 and 180 days prior to the 6-month assessment; two were done less than 30 days prior to the primary effectiveness assessment.

The Sponsor has also reported that 1 subject underwent cardioversion between 6 and 12 months after treatment that resulted in the patient's classification as a success at the long term assessment. That subject had longstanding persistent AF and was a primary effectiveness endpoint failure (in AF at 6 months) but a secondary effectiveness success (in a paced rhythm and off AADs at 12 months). This illustrates the salutary effect of cardioversion on the long-term success at abolishing AF; however, it does not necessarily speak to the primary effectiveness of the device, even though it is highly unlikely that anyone with longstanding persistent AF would have been successfully cardioverted without a substrate-modifying procedure such as an ablation.

Although cardioversions are allowed according to protocol, and are even considered standard-of-care for patients after ablative procedures, as the cardioversion is performed more and more closely in time to the rhythm assessment, it becomes difficult to determine the relative effect of the device versus the cardioversion. FDA's current perspective is that cardioversions may be performed in the first three months following an ablation procedure. Any cardioversions performed after that point are considered to be effectiveness failures. In the ABLATE study, there was 1 primary effectiveness success that underwent cardioversion after 3 months of follow-up within 90 days of the primary effectiveness assessment. An updated post-hoc primary effectiveness endpoint calculation is presented in the following table considering this additional failure.

	All Treated	**Non-Paroxysmal**
Primary Effectiveness Endpoint	**% (n/N) [97.5% BCI]**	**% (n/N) [97.5% BCI]**
Primary Success at 6 months, *no cardioversions after 3 months*	72% (36/50) [0.583,1.00]	71.7% (33/46) [0.574, 1.00]

Table 23. Primary Effectiveness Endpoint Considering Late Cardioversions

The posterior distributions of p_T, AF-free and off AADs at 6 months considering late AAD washout are shown in Figure 13 in section 7.9.5 below.

7.9.3 Lesion Set Deviations

The literature on both surgical ablation during mitral valve operations and theoretical models of AF indicates that the presence of specific lesions has a profound effect on

mid- and long-term rhythm outcomes.[*] In particular, the mitral annulus lesion is needed to maximize the rate of freedom from AF.

According to the study protocol, 6 of 9 of the ablative lesions were to be created only with the Synergy Ablation Clamp. As reported by the Sponsor, there were several deviations from this scheme. Although only 4% of all lesions (24/550 lesions in 55 subjects) were performed with device(s) or techniques other than the Synergy Ablation Clamp or not performed at all, this occurred in about 25% of subjects (14/55 treated subjects and 13/51 non-paroxysmal subjects). An accounting of these deviations is shown in the tables below on a per-lesion and per-patient basis, respectively. Additional details on these deviations are presented in the Sponsor's executive summary.

Lesion	Deviations	Alternative Method Used	Lesion not Performed
Pulmonary veins	0	0	0
Box lesion - Floor	8	Cut & Sew (6) RF Pen (1)	1
Box lesion – Roof	2	RF Pen (1)	1
Mitral valve annulus*	2	Cryoablation alone used (1)	1
LA appendage	3	Cryoablation (2)	1
Tricuspid valve**	1	0	1
SVC-to-IVC line	1	0	1
Free wall	5	0	5
RA appendage**	2	0	2

*lesion must be initiated with the clamp but can be completed by another modality

**lesion can be performed by any method

Table 24. Lesion Set Deviations Presented by Lesion

Number of deviations per patient	Number of patients	Note
Patients with only 1 deviation	12	9 subjects had a lesion performed with an alternative method 3 subjects had a lesion omitted
Patients with > 1 deviation		
4 deviations	1	In this patient 2 lesions were performed with an alternative method and 2 were omitted
8 deviations	1	This subject was classified has having paroxysmal AF. Only pulmonary vein isolation was performed on this patient.

[*] {Dang et al., 2005, Ann Biomed Eng, 33, 465-74; Fassini et al., 2005, Journal of Cardiovascular Electrophysiology, 16, 1150-1156; Gillinov and Saltman, 2007, Semin Thorac Cardiovasc Surg Seminars in thoracic and cardiovascular surgery, 19, 25-32; Gillinov et al., 2006, The Annals of Thoracic Surgery, 82, 502-514}

Table 25. Lesion Set Deviations Per Patient

One of these patients was classified as having paroxysmal AF. For this patient, only pulmonary vein isolation was performed. All other deviations were reported for patients classified as having non-paroxysmal AF.

Per the protocol, the mitral annulus lesion may be started with the Synergy Ablation Clamp and completed with either cryothermy or RF pen. As noted in the table above, which includes those lesions reported by the Sponsor to be considered as deviations, there was one case in which cryothermy was used alone for the entire mitral lesion. As the literature strongly suggests, lesions to the mitral annulus should be performed in all cases of ablation with mitral valve surgery. [*] It has yet to be determined if it is so important in other types of concomitant procedures.

The protocol also indicates that right tricuspid valve annulus lesion and the right atrial appendage to tricuspid annulus lesion can be completed with the Synergy Ablation Clamp, cryothermy, AtriCure Transpolar Pen or surgery. It is notable that the Synergy Ablation Clamp was not used at all for these lesions in approximately 30% of cases where these lesions were attempted.

The reasons provided by the Sponsor for using an alternative method to perform any of the required lesions include:

- Physician attempting to limit the number of maneuvers in the procedure (7 lesions; 7 patients)
- Pre-existing scarring from an existing ICD lead made use of the device challenging (2 lesions; 1 patient)
- Physician practice (2 lesions; 2 patients)

In cases where lesions were not performed, the Sponsor indicates that there were anatomical constraints or limited atrial space for performing those lesions.

Interpretation of study results is difficult for subjects where the full lesion set was not performed using the AtriCure Synergy Ablation System. A conservative approach to interpretation could be to assume that an alternative method was used, either cryoablation or cut-and-sew, because the lesion could not be performed with the AtriCure Synergy Ablation System; those cases would be interpreted as effectiveness failures. For cases where lesions were not performed at all, these could be considered to represent a worst-case for effectiveness. These cases can be analyzed using an intent-to-treat approach. The following results classify those 10 (8 evaluable) patients in which an alternative method was used to create at least one lesion as effectiveness failures.

[*] Gillinov, 2005, Curr Opin Cardiol, 20, 107-14

The primary effectiveness results considering use of alternative methods as failures are presented below in Figure 13 in section 7.9.5 along with the posterior distributions of p_T.

	Treated	Non-Paroxysmal
Primary Effectiveness Endpoint	**% (n/N) [97.5% BCI]**	**% (n/N) [97.5% BCI]**
Primary Success at 6 months, *lesions created with device(s) as specified in the study protocol*	58% (29/50) [0.422, 1.00]	56.6% (26/46) [0.422, 1.00]

Table 26. Primary Effectiveness Endpoint Considering Lesion Set Deviations

FDA Commentary: FDA seeks input from the advisory panel regarding how effectiveness of the AtriCure Synergy Ablation System should be interpreted considering that 8 of 50 evaluable patients required additional methods to complete the lesion set, and how this level of effectiveness factors into the approvability of the device. In assessing approvability of the device, it is also important to consider whether instructions for use can be written for performing the ablation procedure with the study device to treat AF considering the observed non-compliance with the ablation protocol.

7.9.4 Consideration of Current Clinical Guidelines

Definitions of AF recurrence have changed since the approval of the ABLATE clinical IDE study. In the ABLATE study, freedom from AF was defined as freedom from episodes < 5 minutes in duration and no more than 1 hour total AF duration in 24 hours. Current guidelines consider recurrence of AF to include any episode of AF, atrial flutter, or atrial tachycardia lasting longer than 30 seconds. Ideally, rhythm status is measured with a 24-48 hour Holter monitor. In the ABLATE study, the 6 month evaluation was primarily performed with a 24 hour Holter recording. The 12 month (or greater) evaluation was primarily performed with a 48 hour Holter recording. The results in the table below include 2 cases of atrial flutter greater than 5 minutes (non-paroxysmal subjects) and 1 case of AF between 30 seconds and 5 minutes (paroxysmal subject) at the 6 month evaluation. At 12 months, the results in the table include one additional case of atrial flutter and one additional case of atrial tachycardia (counting these cases as failures), compared to results using the original ABLATE definitions.

Effectiveness Endpoint	**Treated % (n/N) [97.5% BCI]**	**Non-Paroxysmal % (n/N) [97.5% BCI]**
Effectiveness Evaluable at 6-Month Follow-up	**N=50**	**N=46**
Free of AF, AFL, and AT and off AADs	70.0% (35/50) [0.562, 1.00]	71.7% (33/46) [0.574, 1.00]
Free of AF, AFL, and AT	78.0% (39/50)	78.3% (36/46)

Effectiveness Endpoint	Treated % (n/N) [97.5% BCI]	Non-Paroxysmal % (n/N) [97.5% BCI]
Effectiveness Evaluable at 12-Month Follow-up or greater (Mean Follow-up is 641 days)	**N=48**	**N=45**
Free of AF, AFL, and AT and off AADs	58.3% (28/48)	57.8% (26/45)
Free of AF, AFL, and AT	70.8% (34/48)	68.9% (31/45)

Table 27. Effectiveness Results Considering 2007 HRS Statement Definitions of Freedom from AF

7.9.5 Overall Ancillary Effectiveness Analysis

Taking into consideration the factors above,

- inadequate drug washout at the 6 month evaluation period,
- cardioversions performed after 3 months, post-procedure
- use of a method other than the Synergy Ablation Clamp to create lesions, and
- evolving definitions of ablation success,

the following analysis presents summary results for the primary and secondary effectiveness endpoints.

	Treated	Non-Paroxysmal
Effectiveness Endpoint	**% (n/N) [97.5% BCI]**	**% (n/N) [97.5% BCI]**
Effectiveness Evaluable at 6-Month Follow-up	N=50	N=46
Free of AF, AFL, and AT and off AADs	**50% (25/50)* [0.366, 1.00]**	**50% (23/46)* [0.361, 1.00]**
Failure by rhythm AF Atrial flutter	11 (9) (2)	10 (8) (2)
Failure by AAD Inadequate drug washout	6 (3)	5 (3)
Failure by CV between 3 and 6 months	4	4
Failure by alternate method for lesion creation	8	8
Free of AF, AFL, and AT	**58.0% (29/50)**	**56.5% (26/46)**
Failure by rhythm AF Atrial flutter	11 (9) (2)	10 (8) (2)
Failure by late CV	4	4
Failure by alternate method for lesion creation	8	8

* Overall rate can not be computed by simple summation of counts for individual failure modes as several subjects failed by more than one mode: Late CV and AAD (1); Rhythm (AFL) and AAD (1); Late CV and Rhythm (AF) (2).

Table 28. Primary and Secondary Effectiveness Endpoints Considering Late AAD Washout, Late Cardioversion, Lesion Set Deviations, and Current Clinical Definitions

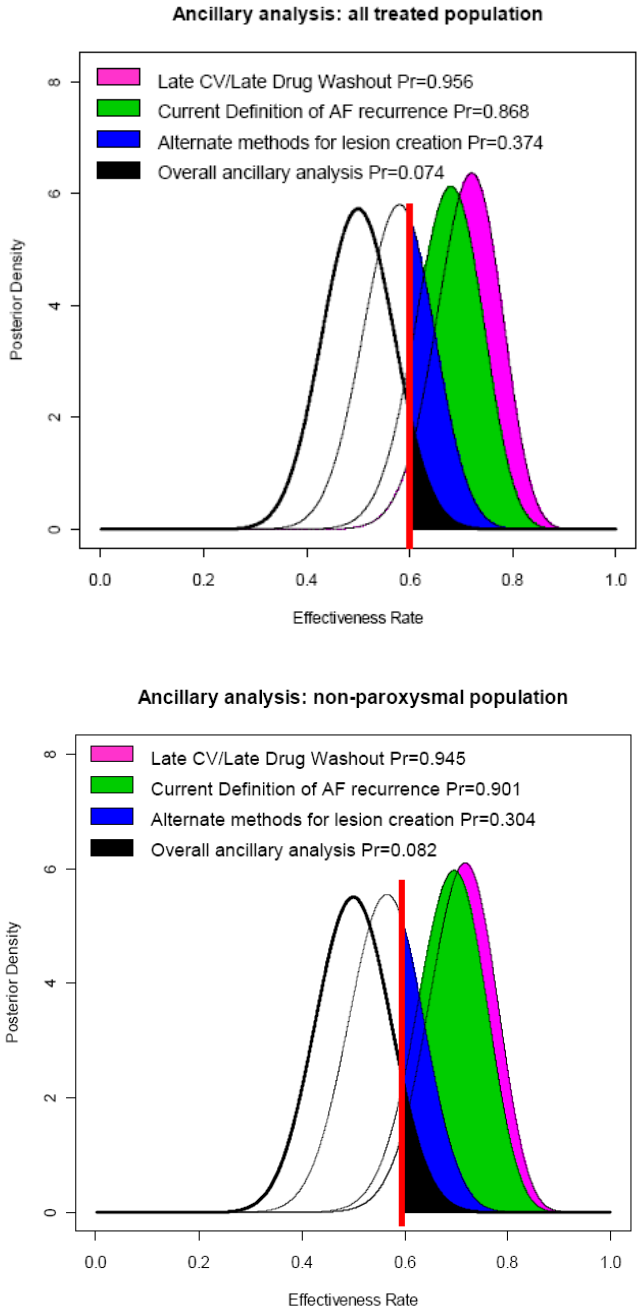

Figure 13. Posterior Distributions for All Treated Subjects (upper) and Non-Paroxysmal Subjects (lower). In these plots, the vertical red line shows the 60% performance goal. Posterior probabilities for success are given in the legend for each of the curves.

FDA Commentary: The table above provides summary information for the effectiveness results for the ABLATE pivotal study considering the several factors discussed above. As the sample size of the ABLATE pivotal study is small, although the occurrence of failures due to each of the modes described individually is low, when combined, the observed effectiveness is significantly decreased. FDA is seeking panel input regarding the

relative significance of each of the factors described, and whether the risk/benefit profile of the device supports approval of the desired indication when all factors and their weight are considered.

8 ADDITIONAL DATA SOURCES

The Sponsor conducted its ABLATE clinical study per the pre-specified protocol. However, at the time that the Sponsor had conducted the interim analysis and presented to the FDA their plans to submit a PMA, the Agency was concerned that deviations or other concerns with individual data points might have a large impact on interpretation of results considering the small final sample size. As such, FDA and the Sponsor discussed ways to bolster the data. These included the creation of registry study and presentation of data from other sources that would reflect the study device's use in similar subject populations. The Sponsor volunteered three such sources: the RESTORE IDE pivotal trial, the Washington University AF ablation database, and the Baylor-Plano AF ablation database. Brief descriptions of each of those data sources and results are described below. Some additional detail on these data sources is provided in Appendix B to this executive summary. For complete details on each of these data sources, please refer to the Sponsor's executive summary and supporting appendices.

8.1 Brief Description of Data Sources

8.1.1 ABLATE AF

In addition to the Sponsor's pivotal study, the Sponsor has initiated an ongoing registry to obtain additional supportive data for the use of the AtriCure Synergy Ablation System. This registry, called ABLATE AF, is enrolling subjects with persistent or longstanding persistent AF who are undergoing ablation with the test device along with a concomitant cardiac surgical procedure. The inclusion and exclusion criteria are identical to those in ABLATE, with the exception that the inclusion criteria specify persistent or longstanding persistent AF rather than permanent AF. In addition, the protocol specifies that a 48-hour rather than 24-hour Holter recording be performed at both 6 and 12 months.

Currently there are 15 centers actively enrolling; 3 centers have actually enrolled subjects. The safety data have been monitored and adjudicated through 30-day follow-up for a subset of patients. A core lab assessed 6-month rhythm results and source documentation was used for assessment of AAD status. As of August 31, 2011, 32 subjects have been enrolled with 14 subjects monitored and adjudicated through 30 days. One (1) of these subjects was classified as having paroxysmal AF. Primary safety data are available for 13 non-paroxysmal AF subjects; primary effectiveness data are available for 11 non-paroxysmal AF subjects.

8.1.2 RESTORE

RESTORE, conducted under IDE G020237, was a multi-center, prospective, non-randomized study with case-matched controls to assess the safety and effectiveness of the AtriCure Bipolar System in the treatment of subjects with continuous atrial fibrillation.[*] The ablation system components were identical except for the clamps, which were determined to be substantially equivalent for indications of "ablation of cardiac tissue" by K101174.

The RESTORE and ABLATE hypotheses were quite similar, with 30-day primary safety and 6-month primary effectiveness endpoints. However there were differences in the eligibility criteria, the specific definition of the composite primary safety endpoint, and that rhythm status was primarily measured with ECG. The problem that led to RESTORE's abandonment was the use of a matched, concurrent, control cohort to determine device safety. Enrollment was targeted at 113 subjects per group, but by the time of RESTORE's termination 39 subjects had been treated with the device, and only 5 had been enrolled in the control arm. Of these 39 subjects, 3 were determined to have paroxysmal AF. Primary safety data are available for the 36 non-paroxysmal AF subjects; primary effectiveness data at 6 months are available for 28 non-paroxysmal AF subjects.

Although not part of the original RESTORE protocol, as part of the effort to obtain supportive data for their PMA, the Sponsor retrospectively obtained 12-month (or later) rhythm status data for 24 of the 36 non-paroxysmal AF subjects.

8.1.3 Institutional Databases

In addition to the Sponsor's own IDE studies, the Sponsor queried databases at the Heart Hospital of Plano (Baylor-Plano) and Washington University (Wash U). Baylor-Plano maintains a database of subjects that receive a cardiac surgical procedure. Wash U maintains a database that tracks all patients undergoing the Maze procedure and utilizes the STS database system with extended variables. Wash U also maintains a follow-up database that tracks AF status with Holter monitoring or pacemaker interrogation performed at 6 month intervals.

The Baylor-Plano database was queried to extract data from patients operated upon between February 2007 and September 2008. The Wash U database was queried to extract data from January 2002 through April 30, 2010. For each data source, consecutive eligible patients have been included in the analysis. Both the Isolator and Synergy Ablation Clamps were represented. The following criteria were used to query the databases:

- Patients with non-paroxysmal AF undergoing Maze IV

[*] Fuster et al., 2001, Circulation, 104, 2118-50

- AF procedure using AtriCure Bipolar System
- Concomitant cardiac surgical procedure

The queries yielded 8 subjects from the Baylor-Plano database and 56 subjects from the Wash U database.

8.2 Results from Additional Data Sources

In order to take advantage of all of the data sources presented by the Sponsor, composite tables of each source's results are presented below. The data are not pooled, as poolability is not justified due to differences in subject population, differences in endpoint definitions, and heterogeneity of actual follow up times. Rather, the data are juxtaposed to provide a comparison. These tables report results for non-paroxysmal subjects only. The table below summarizes the data available from all data sources.

Source	Primary Safety Endpoint Data	6 Month Efficacy Data	≥ 12 month Efficacy Data
ABLATE	51	46	45
ABLATE AF	13	11	0
RESTORE	36	28	24
Baylor-Plano	8	2	3
Wash U	56	47	46
TOTAL	164	134	118

Table 29. Number of Non-Paroxysmal Subjects in All Data Sources

8.2.1 Primary Safety Endpoint

The primary safety endpoint for all five data sources is a composite of:

- Death within 30 days, or beyond 30 days if procedure-related,
- Stroke or TIA with permanent residual disability,
- Bleeding more than 2 units PRBC with re-operation, and
- Myocardial infarction

	ABLATE	ABLATE AF	RESTORE	Wash U	Baylor-Plano
Sample Size (N)	51	13	36	56	8
Primary safety	9.8% (5/51)	0% (0/13)	8.3% (3/36)	14.3% (8/56)	25.0% (2/8)
Death	3.9% (2/51)	0% (0/13)	5.6% (2/36)	3.6% (2/56)	12.5% (1/8)
Bleeding	3.9% (2/51)	0% (0/13)	8.3% (3/36)	8.9% (5/56)	24.0% (2/8)
Stroke/TIA	2.0% (1/51)	0% (0/13)	0.0% (0/36)	1.8% (1/56)	0% (0/11)
MI	0% (0/51)	0% (0/13)	0.0% (0/36)	0% (0/56)	0% (0/11)

Table 30. Primary Safety Endpoint for All Data Sources (Non-Paroxysmal Subjects)

8.2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint for all studies is freedom from AF, off AADs, at 6-months.

	ABLATE	ABLATE AF	RESTORE	Baylor-Plano	Wash U
AF Free @ 6 months, no AADs	73.9% (34/46)	81.8% (9/11)	64.3% (18/28)	0% (0/2)	74.5% (35/47)

Table 31. Primary Effectiveness Endpoint for All Available Data Sources (Non-Paroxysmal Subjects)

FDA commentary: Although RESTORE, ABLATE and ABLATE AF defined "freedom from AF" as no episode of AF lasting longer than *5 minutes*, Wash U used the more stringent definition of no episode of AF, atrial flutter, or atrial tachycardia lasting longer than *30 seconds*. Although individual samples are small, the results appear reasonably consistent.

8.2.3 Secondary Endpoints

FDA requested uniformity for the several secondary endpoints:

- Freedom from AF at 6-months regardless of AADs,
- Freedom from AF at 12-months (or greater), off AADs, and
- Freedom from AF at 12-months (or greater), regardless of AADs.

Because some of these data were gathered retrospectively, after interactions between FDA and the Sponsor, the 12-month-or-greater information was gathered at a median of 658 days for ABLATE and 439 days for RESTORE. (The 12-month data for Wash U was gathered at 12 months, as this was a prospective protocol at that institution.)

	ABLATE	ABLATE AF	RESTORE	Baylor Plano	Wash U
AF Free @ 6 months	82.6% (38/46)	90.9% (10/11)	81.8% (27/33)	50.0% (1/2)	91.5% (43/47)
AF Free @ >=12 months, no AADs	62.2% (28/45)	--	45.8% (11/24)	0% (0/3)	84.8% (39/46)
AF Free @ >=12 months	73.3% (33/45)	--	66.7% (16/24)	0% (0/3)	91.3% (42/46)

Table 32. Secondary Effectiveness Endpoints for all Available Data Sources (Non-Paroxysmal Subjects)

FDA Commentary: The Sponsor has obtained and provided data from multiple sources in support of its PMA. Individual data sets are similar in size to or smaller than the ABLATE pivotal study. FDA believes that the data sources demonstrate qualitatively similar device performance, considering the differences in patient selection and the limited sample size of each individual data source.

9 POST-APPROVAL STUDY

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The FDA review team has made the recommendation that if the AtriCure Synergy Ablation System is approved, a post-approval study (PAS) or studies should be required as a condition of approval for this second-of-a-kind device. Through review of the premarket data, FDA has identified the following postmarket concerns and recommends that a PAS be conducted to assess the long-term performance of the device in a representative population of providers and patients.

The Sponsor's PAS protocol is currently under development. The last formal protocol provided was submitted on September 9, 2011. An overview of the proposed PAS protocol is provided below. Since then, progression of the PAS protocol has been accomplished interactively.

9.1 Overview of Proposed Post-Approval Study

9.1.1 Study Design and Study Population

The Sponsor proposes a prospective observational post-approval study, in order to evaluate the safety and effectiveness of the device in a real-world setting over the long-term. Consecutive patients will be enrolled who meet the study eligibility criteria, which include presence of non-paroxysmal atrial fibrillation, are scheduled to undergo coronary artery bypass surgery and/or cardiac valve surgery on cardiopulmonary bypass, and are at least 18 years old. The study will enroll approximately 350 subjects at up to 50 centers.

9.1.2 Hypotheses

9.1.2.1 Effectiveness hypothesis

The Sponsor proposes testing an effectiveness hypothesis that states that freedom from AF at three years will be greater than 47.8% – thus using an effectiveness success criterion of 47.8% freedom from AF at three years. They arrive at this success criterion by:

- citing a success rate of 57.8% seen at an average of 20 months post-procedure in non-paroxysmal subjects treated under the ABLATE trial;

- subtracting 10%, citing a similar subtraction used in the ABLATE trial to establish effectiveness criteria.

9.1.2.2 Safety hypothesis

The Sponsor proposes testing a safety hypothesis that states that the combined serious ablation procedure- and device-related adverse event rate will be less than 17.5% – thus using a safety success criterion of 17.5% within 30 days or prior to hospital discharge. They arrive at this success criterion by:

- citing a serious device- or ablation procedure-related adverse event rate for non-paroxysmal AF subjects from the combined IDE ABLATE trial and ABLATE AF clinical trials of 12.5%.
- adding another 5%, citing a similar addition used in the ABLATE trial to establish safety criteria.

9.1.3 Primary Endpoints

The primary effectiveness outcome is freedom from atrial fibrillation (AF) at 12, 24, and 36 months post-procedure. Freedom from AF is defined as no episodes of AF, atrial flutter or atrial tachycardia lasting more than 30 consecutive seconds, as determined by 48 hour Holter monitor, while off Class I and Class III anti-arrhythmic drugs for at least four weeks.

The primary safety outcome is the proportion of patients who experience either a serious ablation procedure- or device-related adverse events within 30 days or prior to hospital discharge, whichever is later. A serious adverse event is defined as an event that is life threatening, requires hospitalization or prolongation of an existing hospitalization, results in significant disability or incapacity or requires intervention to prevent any of the above.

9.1.4 Secondary Endpoints

Secondary endpoints include:

- The proportion of patients free from AF, regardless of AAD usage, as determined by an independent core lab assessment of 48 hour Holter recording performed at a minimum of 12, 24 and 36 months postoperatively.
- Major adverse events occurring post-operatively within 30 days of procedure or hospital discharge (whichever is later) including:
    - Death (includes deaths after 30 days or hospital discharge if death is procedure related).
    - Stroke (resulting in significant permanent disability)
    - TIA
    - Myocardial infarction

    - Excessive bleeding (requiring >2 units of blood replacement and surgical intervention).
- Serious device- and ablation procedure-related adverse events by type of procedure.
- All serious adverse events that are reported in the study.

FDA Commentary: FDA generally agrees with the proposed study design, the study population, and the study endpoints. However, FDA has concerns about the methods used to determine the effectiveness and safety success criteria.

The effectiveness success criterion used in the premarket study was 60% freedom from atrial fibrillation at six months. The Sponsor is proposing that the success criterion at three years be reduced to 47.8%, based on premarket data and a subtraction of 10%. However, success criteria should be based on clinical acceptability. In other words, the Sponsor's proposed success criterion of 47.8% freedom from AF at three years can be justified only by explaining why that is a clinically acceptable result, considering the benefit to the patient vs. the risks of undergoing the procedure.

Similarly, the Sponsor's proposed success criterion for their safety endpoint, of 17.5% serious ablation procedure- and device-related adverse events, is based on data from the premarket study, with an addition of 5%. Yet the Sponsor provides no justification for that success criterion based on clinical acceptability. In addition, the Sponsor proposes that the investigator, rather than an independent adjudication entity, would adjudicate adverse events. FDA believes the PAS design should incorporate a Clinical Events Committee.

FDA seeks input from the panel on the clinical acceptability of the proposed performance goals and how safety events should be adjudicated.

10 CONCLUSIONS

The Sponsor is proposing an indication for the use of the AtriCure Synergy Ablation System in the treatment of persistent or longstanding persistent AF in the concomitant surgical setting. Several attempts have been made to assess device safety and effectiveness for this indication. RESTORE, a case-control study, failed because of poor enrollment. ABLATE utilized a Bayesian adaptive design to enroll only the minimum number of subjects necessary to meet the study endpoints. Although this required only 55 subjects, retrospective examination of subject rhythm data resulted in some disqualifications. Even when considering additional data from the Washington University and Baylor-Plano databases, only 175 subjects are presented for evaluation. All available data are consistent with regard to observed safety and effectiveness rates, although differences between the populations and results exist. There appears to be no safety signal in this limited cohort of patients.

When examining the primary safety and effectiveness results for all subjects enrolled in ABLATE, which includes subjects with paroxysmal AF, the trial appears to have succeeded. However, when considering only the non-paroxysmal patients, neither the primary safety nor effectiveness endpoints are met, although the results are close, as one could expect because of the adaptive nature of the trial design. The supporting data from ABLATE AF, RESTORE, Washington University, and Baylor-Plano provide similar results.

Several important questions therefore remain, concerning issues of trial enrollment, subject management, and results interpretation. More specifically, FDA requests panel input regarding:

- interpretation of study results for the targeted population considering several factors, such as cardioversions performed, late evaluations due to AAD use, definitions of freedom of AF per current guidelines, and non-compliance with the surgical ablation protocol;
- the appropriateness of the study design for the targeted population;
- interpretation of the overall data and rendering an approvability recommendation; and finally,
- the appropriateness of the endpoints and performance goals for the proposed post-approval study protocol.

11 APPENDIX A – WHAT IS BAYESIAN STATISTICS?

Bayesian statistics is an approach for learning from evidence as it accumulates. The Bayesian approach uses Bayes' Theorem to combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available.

When good prior information on clinical use of a device exists, the Bayesian approach may enable this information to be incorporated into the statistical analysis of a trial. However, the Bayesian approach is useful even in the absence of prior information. For example, the approach can accommodate adaptive trials (e.g., interim analyses or change to sample size) and even some unplanned, but necessary trial modifications. Other potential uses include adjustment for missing data, sensitivity analysis, multiple comparisons, and optimal decision making.

11.1 The prior distribution

As an illustration, suppose that the Greek letter **θ** represents a parameter in a clinical trial. The initial knowledge about **θ** prior to data collection is represented by the prior distribution for **θ**, which we denote in symbols as P(**θ**). Suppose **θ** is the rate of a serious adverse event. Its possible values lie between 0 and 1. The prior distribution might give preference to lower values of **θ** (see Figure 1). The probability that **θ** takes on any particular set of values is determined by the area under the curve for those values. So the prior probability that the adverse event rate **θ** is greater than 0.4 (the shaded area) is about 0.38.

An *informative* prior distribution gives preferences to some values of the quantity of interest as being more likely than others (See Figure 1). Lack of preference among the values or lack of information can be represented through a *non-informative* prior distribution (e.g., a uniform prior which indicates no preference for any value of **θ**).

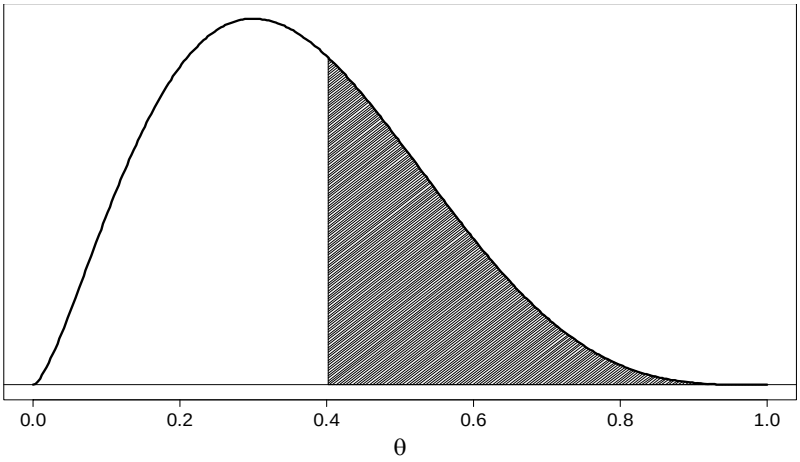

Figure 14. Example of a unimodal, right-skewed prior distribution for a serious adverse event rate, denoted by θ. The prior probability that θ is greater than 0.4 (the shaded area) is about 0.38.

11.2 The likelihood of the observed data

Now suppose outcomes have been obtained from a clinical trial. The likelihood function is a mathematical representation of the relationships between observed outcomes and the parameter **θ**. The likelihood function can be expressed in symbols by P(data |**θ**), which is the conditional probability of observing the data given a specific value of the parameter **θ**, for each possible value of **θ**.

11.3 The posterior distribution

The final objective is to obtain the posterior distribution, the probabilities of the possible values of the parameter **θ** conditional on the observed data, which can be denoted in symbols as P(**θ**| data). Bayes' theorem is used to update the prior distribution for **θ,** P(**θ**), via the likelihood, P(data|**θ**), to obtain the posterior distribution for **θ**, P(**θ**|data). At the conclusion of the trial, the information about **θ** is summarized by this posterior distribution, and Bayesian inferences are based on it.

As an example, Figure 2 shows the posterior distribution that would be obtained if we started with the prior shown in Figure 1 and observed data with 1 adverse event in 10 patients. Since the adverse event rate observed in these patients is 0.10, the distribution has shifted further to the left (that is, it now favors even lower values for **θ**). The posterior probability that **θ** is greater than 0.4 (the shaded area) is about 0.04. The probability that the adverse event rate is greater than 0.4 has been reduced from about 0.38 (the prior probability) to about 0.04 (the posterior probability) by the favorable trial results.

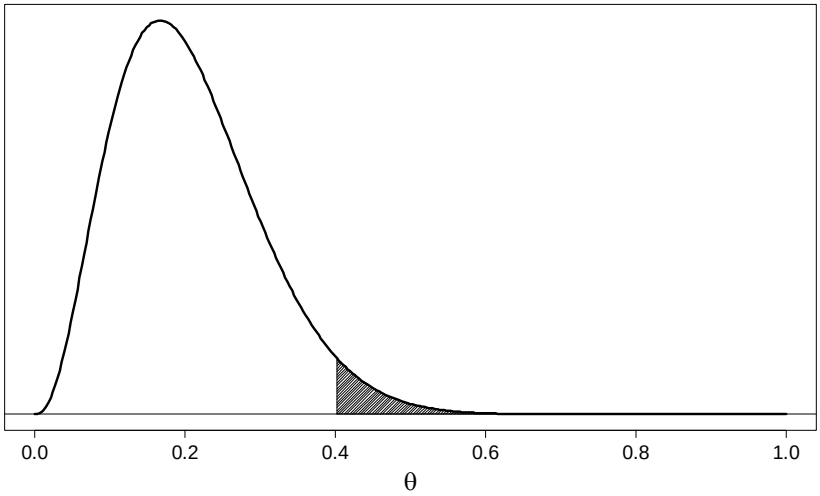

Figure 15. Example of a unimodal, right-skewed posterior distribution for a serious adverse event rate, denoted by θ, after observing one adverse event in 10 patients and updating the prior probability in Figure 1. The posterior probability that θ is greater than 0.4 (the shaded area) is about 0.04.

The posterior distribution that has been obtained today may serve as a prior distribution when more data are gathered. The more information that is accrued, the less uncertainty there may be about the posterior distribution for **θ**. If enough data are

collected, the relative importance of the prior distribution will be negligible compared to the likelihood.

Bayesian inferences are based on the posterior distribution. For example, a Bayesian decision procedure might rule out a set of parameter values if the posterior probability of the parameter values (given the observed data) is small.

A pre-specified decision rule is used to demonstrate hypotheses that define safety and effectiveness with reasonable assurance. For Bayesian trials, one common type of decision rule considers that a hypothesis has been demonstrated (with reasonable assurance) if its posterior probability is large enough (e.g., 95 or 99 percent).

11.4 The predictive distribution

The Bayesian approach allows for the derivation of a special type of posterior probability; namely, the probability of unobserved outcomes (future or missing) given what has already been observed. This probability is called the *predictive probability*. Collectively, the probabilities for all possible values of the unobserved outcome are called the predictive distribution. Predictive distributions have many uses, including determining when to stop a trial (based on predicting outcomes for patients not yet observed) or adjusting trial results for missing data (imputation).

These uses are discussed in more detail below in **Analyzing a Bayesian Clinical Trial**.

11.5 Exchangeability

Exchangeability is a fundamental concept underlying statistical inference. It can be of particular importance in Bayesian trials. Formally, we would say that units (patients or trials) are considered *exchangeable* if the probability of observing any particular set of observations on those units is invariant to any re-ordering of the units.

Exchangeability of patients

In a clinical trial, patients within the trial are usually assumed to be exchangeable. Under exchangeability, patient outcomes are not expected to depend on the order in which the patients were enrolled, the order in which the outcomes are observed, or any other re-indexing or re-numbering of the patients.

If patients in the trial are exchangeable with patients in the population from which they were sampled (e.g., the intended use population), then inferences can be made about the population on the basis of data observed on the trial patients. Thus, the concept of a *representative sample* can be expressed in terms of exchangeability.

Exchangeability of trials

For a Bayesian clinical trial, another level of exchangeability might be assumed. Namely, the trial can be assumed to be exchangeable with other previous trials when the previous trials are considered to be good prior information. The assumption of trial exchangeability enables the current trial to “borrow strength” from the previous trials, while acknowledging that the trials are not identical in all respects. Thus,

exchangeability is important in the development of realistic models for combining trial data with prior information.

11.5.1 Bayesian Adaptive Designs

Adaptive designs use accumulating data to decide how to modify certain aspects of a trial according to a pre-specified plan without undermining the validity and integrity of the trial. Adaptive trial designs have the potential to provide optimal statistical inference and to improve quality, speed and efficiency of decision making.

An adaptive Bayesian clinical trial can involve interim looks to adapt the sample size (to stop or to continue patient accrual) or interim looks for the purpose of possibly stopping the trial early either for success, futility, or harm.

A purely Bayesian approach would allow for continuous design adaptation as the trial take place. However, in order to maintain the integrity of the trial while minimizing operational biases, the Bayesian adaptive trial should be adaptive *by design*.

11.6 Analyzing a Bayesian Clinical Trial

The results, conclusions, and interpretation of a Bayesian analysis all rely on the posterior distribution. Consequently, results and conclusions for a Bayesian trial are based only on the posterior distribution.

11.6.1 Hypothesis testing

For Bayesian hypothesis testing, one can use the posterior distribution to calculate the probability that a particular hypothesis is true, given the observed data.

11.6.2 Interval estimation

Bayesian interval estimates are based on the posterior distribution and are called *credible intervals*. If the posterior probability that an endpoint lies in an interval is 0.95, then this interval is called a 95 percent *credible interval*.

11.6.3 Predictive probabilities

Uses of predictive probabilities include the following:

Deciding when to stop a trial

One can use a predictive probability at an interim point as the rule for stopping the trial. If the predictive probability that the trial will be successful is sufficiently high (based on results at the interim point), the trial may be stopped and declared successful.

Exchangeability is a key issue here: these predictions are reasonable only if you can assume the patients who have not been observed are exchangeable with the patients who have. This assumption is difficult to formally evaluate but may be more plausible in some instances (e.g., administrative censoring) than others (e.g., high patient drop-out).

Predicting outcomes for future patients

One may also calculate the predictive probability of the outcome of a future patient, given the observed outcomes of the patients in a clinical trial, provided the current patient is exchangeable with the patients in the trial.

Predicting (imputing) missing data

One may use predictive probabilities to predict (or *impute*) missing data, and trial results can be adjusted accordingly. The adjustment depends on the assumption that patients with missing outcomes follow the same statistical model as patients with observed outcomes. This means the missing patients are exchangeable with the non-missing patients, or that data are *missing at random*.

Predicting a clinical outcome from earlier measurements

If patients have measurements of the same outcome at earlier and later follow-up visits, one can make predictions for the later follow-up visit (even before the follow-up time has elapsed).

11.6.4 Interim analyses

Bayesian interim analyses typically involve the following applications:

Applying posterior probability

One method stops the trial early if the posterior probability of a hypothesis at the interim look is large enough. In other words, the same Bayesian hypothesis test is repeated during the course of the trial.

Applying predictive distribution

Another method calculates at interim stages the probability that the hypothesis test will be successful at the end of accrual and follow-up. This method uses the Bayesian predictive distribution for patients yet to be measured. If the predictive probability of success is sufficiently high, the trial may stop early. If the predictive probability is very low, the trial may stop early for futility.

12 APPENDIX B - SUMMARIES OF ADDITIONAL DATA SOURCES

12.1 ABLATE AF

12.1.1 Description

ABLATE AF is an ongoing clinical registry enrolling subjects with non-paroxysmal AF who are undergoing ablation with the test device along with a concomitant cardiac surgical procedure. The inclusion and exclusion criteria are identical to those in ABLATE, with the exception that the inclusion criteria specify non-paroxysmal AF rather than permanent AF. In addition, the protocol specifies that a 48-hour rather than 24-hour Holter recording be performed at both 6 and 12 months. Currently there are 15 centers actively enrolling; 12 centers have enrolled subjects. The safety data have been monitored and adjudicated through 30-day follow-up for a subset of patients. A core lab assessed 6-month rhythm results and source documentation was used for assessment of AAD status.

12.1.2 Results

12.1.2.1 Subject Accountability

As of August 31, 2011, 32 subjects have been enrolled in the ABLATE AF registry with 14 subjects enrolled at 3 centers monitored and adjudicated through 30 days. Twelve (12) of these 14 subjects have undergone follow-up for evaluation of the primary effectiveness endpoint at 6 months or later and have been monitored through 6 months. One was found to have paroxysmal AF through an independent AF classification assessment described above. The thirteen (13) non-paroxysmal subjects have been followed through 30 days. Eleven (11) have Holter recordings at 6 months. The table below summarizes the available data for the ABLATE AF registry at this time. Additional information on subject accounting can be found in the Sponsor's executive summary. *Note that results presented in this section focus on the non-paroxysmal subjects.*

	ABLATE	ABLATE AF	ABLATE + ABLATE AF
Total Enrollment	55	32	87
AF Classification			
Paroxysmal	4	1	5
Persistent	22	2	24
Longstanding Persistent	29	11	40
Data available for endpoint evaluation			
Evaluable for 30-day Safety Endpoint			
All treated	55	14	69
Non-Paroxysmal	51	13	64
Evaluable for 6-month Effectiveness Endpoint			
All treated	50	12	62
Non-Paroxysmal	46	11	57
Reason not evaluable at 6 months			
Died	4	0	4
Lost to Follow-up	1	0	1
Not yet presented for 6-mo visit	0	2	2

12.1.2.2 Subject Demographics

The ABLATE AF subject demographics are similar to those seen in the other data sources. Because of the small sample size, no statistical comparisons were made. The following table presents key subject characteristics. Please see the Sponsor's executive summary for additional details.

	Mean	**Range**
Age (years)	70.7 ± 7.8	52 – 81
Male	76.9%	
Duration of AF (months)	94.9	12 - 247
AF longer than 1 year	92%	
Ejection fraction (%)	52.5	30 – 65
LA size (cm)	5.4	3 – 7.3

Procedures Performed	**Proportion**
CABG only	38.5%
Valve only	15.4%
Mitral valve	7.7%
Aortic valve	7.7%
Double valve only	7.7%
Mitral/tricuspid	7.7%
CABG + valve	38.5%
CABG + aortic	23.1%
CABG + mitral	15.4%

Table 33. Subject Demographics for ABALTE AF Non-Paroxysmal Subjects

12.1.2.3 Primary Safety

The primary safety endpoint for ABLATE AF is the same as ABLATE. To date, there have been no Major Adverse Events observed in the study, and so the primary safety endpoint rate is 0%.

	ABLATE N=51	**ABLATE AF N=13**	**ABLATE + ABLATE AF N=64**
Primary Safety Endpoint	**% (n/N)**	**% (n/N)**	**% (n/N)**
Composite MAE within 30 days	9.8% (5/51)	0% (0/13)	7.8% (5/64)
Death	3.9% (2/51)	0% (0/13)	3.1% (2/64)
<=30 days	3.9% (2/51)	0% (0/13)	3.1% (2/64)
>30 days, procedure related	0.0% (0/51)	0% (0/13)	0.0% (0/64)
Stroke/TIA	2.0% (1/51)	0% (0/13)	1.6% (1/64)
Stroke (with significant permanent disability)	2.0% (1/51)	0% (0/13)	1.6% (1/64)
TIA	0.0% (0/51)	0% (0/13)	0.0% (0/64)
MI	0.0% (0/51)	0% (0/13)	0.0% (0/64)
Excessive Bleeding (>2 units blood and surgical intervention)	3.9% (2/51)	0% (0/13)	3.1% (2/64)

Table 34. Primary Safety Results for Non-Paroxysmal Subjects

12.1.2.4 Primary Effectiveness

The primary effectiveness endpoint is the same as for ABLATE.

Primary Effectiveness Endpoint	**ABLATE % (n/N) N=46**	**ABLATE AF % (n/N) N=11**	**ABLATE + ABLATE AF % (n/N) N=57**
Primary Success at 6 months	73.9% (34/46)	81.8% (9/11)	75.4% (43/57)
Failure by AAD	8.7% (4/46)	9.1% (1/11)	8.8% (5/57)
Failure by Rhythm	17.4% (8/46)	9.1% (1/11)_	15.8% (9/57)

Table 35. Primary Effectiveness Results for Non-Paroxysmal Subjects

12.1.2.5 Secondary Endpoints

The secondary safety endpoints of MAE through 6 months and any adverse event through 6 months are the same as in the ABLATE study and are reported in the following table.

Secondary Endpoints	ABLATE % (n/N) (N=51)	ABLATE AF [1] % (n/N) (N=13)	ABLATE AF [1] + ABLATE % (n/N) (N=64)
MAE through 6 months	11.8% (6/51)	7.7% (1/13)	10.9% (7/64)
Death	7.8% (4/51)	0.0% (0/13)	6.3% (4/64)
Stroke (with significant permanent disability)	2.0% (1/51)	7.7% (1/13)	3.1% (2/64)
TIA	0.0% (0/51)	0.0% (0/13)	0.0% (0/64)
MI	0.0% (0/51)	0.0% (0/13)	0.0% (0/64)
Excessive Bleeding (>2 units blood and surgical intervention)	3.9% (2/51)	0.0% (0/13)	3.1% (2/64)
Any Adverse Event through 6 months	94.1% (48/51)	84.6% (11/13)	92.2% (59/64)
Any Serious Event	76.5% (39/51)	69.2% (9/13)	75.0% (48/64)
Any Device Related Event	0.0% (0/51)	0.0% (0/13)	0.0% (0/64)
Any Procedure Related Event	15.7% (8/51)	0.0% (0/13)	12.5% (8/64)
Any Serious Device Related Event	0.0% (0/51)	0.0% (0/13)	0.0% (0/64)
Any Serious Procedure Related Event	13.7% (7/51)	0.0% (0/13)	10.9% (7/64)
[1] For ABLATE AF, events > 30 days post index procedure are included based on site reported classification if not yet adjudicated.			

The study secondary effectiveness endpoints are also the same as for ABLATE:

- Freedom from AF at 6-months, regardless of AAD usage,
- AF Burden at 6-months
- Freedom from AF at 12-months, off AADs, and
- Freedom from AF at 12-months, regardless of AAD usage.

Because no subject has yet reached the 12-month follow up point, there are no data for presentation. However the table below presents 6-month freedom from AF, regardless of AAD usage.

	ABLATE N=46	ABLATE AF N=11	ABLATE + ABLATE AF N=57
Secondary Effectiveness Endpoint	**% (n/N)**	**% (n/N)**	
Free of AF, Regardless of AADs*	82.6% (38/46)	90.9% (10/11)	84.2% (48/57)
AF Burden			
= 0 min	82.6% (38/46)	90.9% (10/11)	84.2% (48/57)
<= 5 min	0% (0/46)	0.0% (0/11)	0.0% (0/57)
> 5 min - 1 hr	2.2% (1/46)	0.0% (0/11)	1.8% (1/57)
> 1 hr	15.2% (7/46)	9.1% (1/11)	14.0% (8/57)

Table 36. Secondary Effectiveness Results for Non-Paroxysmal Subjects

* Using the definition of the 2006 Guidelines: "AF free" = no episodes > 5 minutes

FDA Commentary: Regarding the factors affecting interpretability of the data as discussed for the ABLATE study under Section 7.9, the following are observed for ABLATE AF:

Considerations in Data Interpretation	Note
Late Cardioversions	There were no cardioversions performed after 17 days from the index procedure.
Holter Monitoring performed outside of specified window of 180+30 days	• Two were out side of the window (by 9 and 22 days)to allow washout of amiodarone • One subject missed the 6-month visit and the Sponsor used a Holter obtained at 12 months for the 6-month visit reading **There was one case where a telephone assessment at 6 months was used for AAD status evaluation and two non-study Holter monitors performed at 3 months and 142 days to determine that a subject was free of AF, on AADs (a primary effectiveness failure, but secondary effectiveness success)*
Lesion Set Deviations	There were 2 lesions in 2 patients that were performed using other methods, and all lesions were attempted.
Current Clinical Definitions	Per current clinical definitions where AF recurrence is any episode of AF, atrial flutter or atrial tachycardia > 30 seconds, there would be 1 additional failures (1 case of AT of unknown duration)

Considering the cases above as failures would result in 4 additional primary effectiveness failures in ABLATE AF.

FDA Commentary: As the protocols used in ABLATE and ABLATE AF are nearly identical, FDA believes that ABLATE AF provides important additional information. Please see the Sponsor's executive summary for more details regarding the ABLATE AF study subjects and results. The results in ABLATE AF thus far are consistent with the results demonstrated by the ABLATE pivotal study.

12.2 RESTORE

This section presents an overview of the RESTORE IDE study, which was terminated early due to enrollment difficulties. As the Sponsor has not provided all detailed data for the RESTORE cohort separated by AF classification type, results are presented here for all subjects, which include 3 subjects with paroxysmal AF. This abstract of the RESTORE study is meant to provide a brief overview. Additional details can be found in the Panel Pack.

12.2.1 Study Objective

RESTORE, conducted under IDE G020237, was a multi-center, prospective, controlled, non-randomized study to assess the safety and effectiveness of the AtriCure Bipolar System in the treatment of subjects with continuous atrial fibrillation.[*] The ablation system components were identical except for the clamps, which were determined to be substantially equivalent for indications of "ablation of cardiac tissue" by K101174.

The RESTORE and ABLATE hypotheses were quite similar, with 30-day primary safety and 6-month primary effectiveness endpoints. The problem that led to RESTORE's abandonment was the use of a matched, concurrent, control cohort to determine device safety. Enrollment was targeted at 113 subjects per group. However, by the time of RESTORE's termination 39 subjects had been treated with the device, but only 5 had been enrolled in the control arm.

12.2.2 Eligibility Criteria

RESTORE had the same inclusion criteria as ABLATE except that a life expectancy of 2 years (versus 1 year) was allowed, and used the term "continuous" was used instead of "permanent" when classifying AF.

The exclusion criteria were almost identical to ABLATE except that RESTORE allowed previous catheter ablation attempts, WPW subjects, recent MI, emergency surgery, left atria > 8 cm, renal failure, concurrent inotrope and/or IABP use, thoracic radiation, steroid use, or connective tissue disorders.

12.2.3 Study Methods

The RESTORE investigators performed the Cox Maze IV procedure, as in ABLATE (see Figure 4 and Figure 5 above). The subjects were to be followed until discharge, at 30 days, at 3 months, and at 6 months. A 1-year visit was intended only for subjects with evidence of, or "at risk for", PV stenosis.

The subjects were placed on AADs immediately after ablation. Washout was required before the 6-month assessment. Cardioversion was allowed up to 3 times prior to the 3-month visit. The effectiveness assessment was to be conducted by ECG with a subset of subjects undergoing a 24 hour holter monitor.

[*] Fuster et al., 2001, Circulation, 104, 2118-50

12.2.4 Results

12.2.4.1 Subject Accountability

Before it was terminated, RESTORE enrolled 39 treatment subjects from 8 U.S. centers. Thirty-five (35) were followed through the 6-month endpoint. Twenty-six (26) subjects were available for the 12-month assessment.

12.2.4.2 Subject Demographics

Compared to ABLATE, in RESTORE there were more women and the duration of AF was somewhat longer. Neither of these differences was statistically significant.

	Mean	Range
Age (years)	65.9 ± 11.1	31 – 80
Male	46.2%	
Duration of AF (months)	94.2 ± 122.6	3.3 – 622.6
AF longer than 1 year	76.9%	
Ejection fraction (%)	51.4 ± 8.7	35 – 70
LA size (cm)	6.1 ± 1.2	4.0 – 9.8

Procedures Performed	Proportion
CABG	10.3%
Mitral valve, alone/combination	71.8%
Aortic valve alone	5.1%
Tricuspid valve alone	2.6%
CABG + Mitral valve	7.7%
CABG + Double valve	2.6%

Table 37. Subject Demographics for RESTORE

12.2.4.3 Primary Safety Endpoint

The primary safety endpoint for RESTORE was the same as ABLATE with the addition of deep sternal wound infection, pulmonary vein stenosis, and esophageal rupture. An independent physician adjudicator reviewed all adverse events. The rate of composite MAE within the first 30 days was 10.3% (6 events in 4 subjects): two deaths, three excessive bleeding episodes, and one deep sternal wound infection. No testing against the control group was performed.

12.2.4.4 Primary Effectiveness Endpoint

The primary effectiveness endpoint was the same as for ABLATE. Thirty of the 39 enrolled subjects (77%) were considered evaluable at 6 months. By ECG criteria (n=19) or Holter monitoring (n=11)[*], 20 (66.7%) were not in AF and were off AADs, with a 95% lower one-sided exact confidence interval for the primary effectiveness endpoint of

[*] Eleven subjects (11) underwent 24-hour Holter monitoring at 6-months: 72.7% were free of AF.

50.1% - 100%. This exceeded the non-inferiority threshold of 50%. Of the 10 failures, 4 were out of AF but on AADs, and 6 were in AF.

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12.2.4.5 Key Secondary Endpoint Assessments

At the time of surgery:

- Pulmonary vein isolation was evaluated in 18 of the 39 subjects (46%)
    - Isolation was documented in 100%.

At the 6-month follow up visit:

- 82.9% were AF-free regardless of AADs
- AF burden as determined by Holter in 11 subjects (28%)
    - AF lasted 24 hours / day in 3 subjects
    - AF was absent in 8 subjects
- No pulmonary vein stenosis was found in 31 evaluated subjects
- 3 subjects (7.7%) received permanent pacemakers
- 84.6% experienced some type of AE
    - 38.5% experienced an SAE
    - None was attributed to the device

At 12 months, there were 26 subjects available for evaluation. Their data were:

- The mean number of days to assessment was 533.9 ± 190.9 (range 356 – 985)
- Three were evaluated by Holter, 4 by pacemaker interrogation, and 19 by ECG
- 50% were AF-free, and off AADs
- 69.2% were AF-free, regardless of AADs

FDA commentary:

1. PV stenosis, wound infection, and esophageal injury were not part of the ABLATE composite primary safety endpoint.
2. RESTORE employed spot ECG assessments to assess the primary effectiveness endpoint rather than 24-hour Holter recordings. (Holter recordings were performed, but only in 11/35 evaluable subjects.)
3. RESTORE allowed previous catheter ablation attempts, WPW subjects, recent MI, emergency surgery, left atria > 8 cm, renal failure, concurrent inotrope and/or IABP use, thoracic radiation, steroid use, or connective tissue disorders whereas ABLATE did not.
4. FDA requested Holter recordings at 12 months on all possible subjects.
5. RESTORE prohibited cardioversion after 3 months, allowing at least 3 months to elapse before the 6-month assessment. ABLATE allowed cardioversion at any time up to the 6-month visit.
6. To maintain alignment with ABLATE reporting, subjects still within the washout period would be primary effectiveness failures. In this case, there should be 35 evaluable subjects and the primary effectiveness success rate would be 20/35 = 57.1% with a 95% one-sided confidence interval of 41.9% – 100%.
7. As with ABLATE, the RESTORE data show a steady decline in device effectiveness over time.

12.3 Baylor-Plano

12.3.1 Description

The Heart Hospital of Plano maintains a database of all patients who undergo cardiac surgery. The subjects selected for this report were operated between February 2007 and September 2008, in order to exclude anyone who might have been enrolled in ABLATE. The criteria used for subject selection were:

- Non-paroxysmal AF
- Maze IV lesion set
- Ablation with the AtriCure Bipolar System
- Concomitant cardiac surgical procedure

12.3.2 Results

12.3.2.1 Subject Accountability

Eight non-paroxysmal subjects underwent concomitant surgical ablation with the test system during this time period. Minimal data were available at the 6-month point (n=2 subjects available. No independent expert rhythm review was performed. However, in keeping with the data presented from ABLATE and RESTORE, the primary safety endpoint rate was calculated from all treated subjects.

12.3.2.2 Subject Demographics and Procedures Performed

The Baylor-Plano subject demographics are similar to the ABLATE and RESTORE subject demographics; no statistical comparisons were made because of the small population.

	Mean	Range
Age (years)	65.0± 11.9	42 – 76
Male	37.5%	
Duration of AF (months)	43.7 ± 36.8	12 – 84
AF longer than 1 year	50.0%	
Ejection fraction (%)	49 ± 15	45 – 73
LA size (cm)	5.3 ± 0.8	4.4 – 6.9

Procedures Performed	Proportion
CABG	0%
Mitral valve, alone / combination	12.5%
Tricuspid valve	12.5%
Aortic valve alone	0%
Double valve	12.5%
CABG + mitral valve	25.0%
CABG + double valve	25.0%
ASD repair	12.5%

Table 38. Subject Demographics for the Baylor-Plano Database

The details regarding the exact lesions performed for each case are not maintained in the Baylor-Plano database. Also, it is not known precisely what concomitant surgical procedures were undertaken.

12.3.2.3 Primary Safety Endpoint

The primary safety endpoint for the Baylor-Plano database was set equivalent to the ABLATE endpoint: A composite of death, excessive bleeding, and stoke/TIA. There was one death (beyond 30 days, but procedure-related) and two episodes of excessive bleeding (one of whom also died). The composite MAE was therefore 2/11 = 18%.

12.3.2.4 Primary Effectiveness Endpoint

As discussed above, the primary effectiveness endpoint data are only available for two subjects. Neither subject was a primary endpoint success yielding 0% effectiveness at 6 months.

12.3.2.5 Secondary Endpoints

Documentation for confirmation of block was not available for most subjects. For the subjects in whom evaluation of block was documented (not known how many), the Sponsor states that pulmonary vein isolation was confirmed.

FDA commentary:

1. The subject population cannot be confirmed to contain only non-paroxysmal subjects.
2. There are no inclusion or exclusion criteria addressing LV function, atrial size, etc.

12.4 Washington University

12.4.1 Description

Potential subjects were operated on at Washington University over an 8-year period; subjects enrolled in RESTORE were removed from the dataset. The criteria for selection of subjects for this analysis were:

- Non-paroxysmal AF,
- Undergoing Maze IV ablation,
- Using the AtriCure test system, and
- Concomitant cardiac surgical procedure.

12.4.2 Results

12.4.2.1 Subject Accountability

Fifty-six subjects met the analysis criteria. All were available for the 30-day safety assessment. Forty-seven (47) were assessed at 6 months: 5 expired before 6 months, 2 were lost to follow-up, and 2 were not yet at 6 months when the data were harvested. One additional subject was lost to follow-up before 12 months, leaving 46 subjects available at 1 year.

12.4.2.2 Subject Demographics

Although no statistical comparisons with the other data sources were made, the subject demographics are very similar to ABLATE and RESTORE.

	Mean	Range
Age (years)	66.3 ± 10.3	39 – 81
Male	54%	
Duration of AF (months)	92.6 ± 95.1	1 – 480
AF longer than 1 year	79%	
Ejection fraction (%)	50 ± 13	20 – 75
LA size (cm)	5.8 ± 1.3	3.8 – 10.0

Procedures Performed	Proportion
CABG	9%
Mitral valve, alone / combination	67%
Aortic valve alone	2%
CABG and valve	16%
CABG and double valve	2%
Cor triatriatum	2%

Table 39. Subject Demographics for the Washington University Database

12.4.2.3 Primary Safety

The primary safety endpoint was set equivalent to the ABLATE primary safety endpoint. There were 8 composite MAE's for a rate of 14.3%: 2 procedure-related deaths, 1 stroke, and 5 excessive bleeding events. None was attributed to the test device.

12.4.2.4 Primary Effectiveness

ECG's were used to assess 22 of the 47 evaluable subjects (47%) at 6-months; a Holter or permanent pacemaker interrogation was performed for the rest. The definition of failure was a minimum of *30 seconds* of AF, atrial flutter or atrial tachycardia. Under these rules, the primary effectiveness endpoint was successfully met in 35 of the 47 evaluable subjects (74%).

12.4.2.5 Secondary Endpoints

- Acute pulmonary vein isolation was tested in 86% of right-sided veins and 84% of left-sided veins. Exit block was documented in all cases (100%).
- Freedom from AF at 6-months, regardless of AAD usage, was 91% (43/47).
- Freedom from AF at 12-months, off AADs, was 85% (39/46).
- Freedom from AF at 12-months, regardless of AAD usage, was 91% (42/46).

FDA commentary:

1. There are no inclusion or exclusion criteria addressing LV function, atrial size, etc.
2. The definition of "rhythm failure" is shorter than 5 minutes (30 seconds).